

Solidification to improve the biopharmaceutical performance of SEDDS

Opportunities and challenges

Joyce, Paul; Dening, Tahnee J; Meola, Tahlia R; Schultz, Hayley B; Holm, René; Thomas, Nicky; Prestidge, Clive A.

Published in:
Advanced Drug Delivery Reviews

DOI:
[10.1016/j.addr.2018.11.006](https://doi.org/10.1016/j.addr.2018.11.006)

Publication date:
2019

Document Version
Peer reviewed version

Citation for published version (APA):

Joyce, P., Dening, T. J., Meola, T. R., Schultz, H. B., Holm, R., Thomas, N., & Prestidge, C. A. (2019). Solidification to improve the biopharmaceutical performance of SEDDS: Opportunities and challenges. *Advanced Drug Delivery Reviews*, 142, 102-117. <https://doi.org/10.1016/j.addr.2018.11.006>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy

If you believe that this document breaches copyright please contact rucforsk@kb.dk providing details, and we will remove access to the work immediately and investigate your claim.

Solidification to Improve the Biopharmaceutical Performance of SEDDS: Opportunities and Challenges

*Paul Joyce,^a Tahnee J. Dening,^{b,c} Tahlia Meola,^{b,c} Hayley Schultz,^{b,c} René Holm,^{d,e} Nicky
Thomas^{b,c} & Clive A. Prestidge^{b,c*}*

^aDepartment of Physics, Chalmers University of Technology, Gothenburg SE-412 96 Sweden

^bUniversity of South Australia Cancer Research Institute, Adelaide, South Australia 5000, Australia

^cARC Centre of Excellence in Convergent Bio-Nano Science and Technology, University of South Australia,
Mawson Lakes Campus, Mawson Lakes 5095, Australia

^dDrug Product Development, Janssen R&D, Johnson & Johnson, Turnhoutseweg 30, Beerse 2340, Belgium

^eDepartment of Science and Environment, Roskilde University, Roskilde 4000, Denmark

*Corresponding Author. Telephone: +61 8 8302 3569. Fax: +61 8 8302 3683. Email:
clive.prestidge@unisa.edu.au

Abstract

Self-emulsifying drug delivery systems (SED DS) offer potential for overcoming the inherent slow dissolution and poor oral absorption of hydrophobic drugs by retaining them in a solubilised state during gastrointestinal transit. However, the promising biopharmaceutical benefits of liquid lipid formulations has not translated into widespread commercial success, due to their susceptibility to long term storage and *in vivo* precipitation issues. One strategy that has emerged to overcome such limitations, is to combine the solubilisation and dissolution enhancing properties of lipids with the stabilising effects of solid carrier materials. The development of intelligent hybrid drug formulations has presented new opportunities to harness the potential of emulsified lipids in optimising oral bioavailability for lipophilic therapeutics. Specific emphasis of this review is placed on the impact of solidification approaches and excipients on the biopharmaceutical performance of self-emulsifying lipids, with findings highlighting the key design considerations that should be implemented when developing hybrid lipid-based formulations.

Keywords: SED DS; self-emulsifying lipids; solidification; lipid-based drug delivery system; lipid-based formulation; poorly water-soluble drugs; pharmacokinetics; bioavailability; oral delivery.

Table of Contents

1. Introduction.....	5
2. Rationale for Transforming Liquid-SEDDS into Solid Dosage Forms	9
2.1 Improved Solubilisation and Dissolution.....	10
2.2 Controlled Drug Release & Delivery.....	13
2.2.1. Multicomponent Release.....	14
2.2.2. Site-Specific Release.....	15
2.3 Improved Safety	15
2.3.1. Reduced Relative Surfactant Concentrations.....	15
2.3.2. Improved Oxidative Stability.....	16
2.4 Additional Industrial Perspectives	17
3. Design Considerations for the Development of Solid-SEDDS	18
3.1 Solidification Approach	19
3.1.1. Form of precursor lipids.....	21
3.1.2. Solid Dosage Form	22
3.1.3. Thermal Stability of Therapeutic Molecules and Lipid Excipients	23
3.1.4. Drug and Lipid Loading Implications on the Required Dosage	24
3.2 Solidification Excipients	25
3.2.1. Influence of Lipid-Solid Carrier Interactions on Lipid Digestion	27

3.2.2. Influence of Lipid-Solid Carrier Interactions on Drug Dissolution and Absorption.....	31
3.3 Therapeutic Compound	39
3.3.1. Drug-Solid Carrier Interactions	39
4. Future Perspectives for the Successful Development of Solid-SEDDS	40
5. Conclusions	43
6. References	46

1. Introduction

The emergence of lipid-based drug delivery systems (LBDDS) as a leading formulation strategy to improve the biopharmaceutical performance of hydrophobic drugs has been driven by their proven ability to mimic the postprandial (food) effect. LBDDS enhance drug solubilisation during gastrointestinal (GI) processing by creating a lipophilic microenvironment that restricts drug precipitation, while concurrently facilitating drug transport towards intestinal absorption sites [1-3]. In the GI tract, lipase-mediated hydrolysis of digestible lipid excipients stimulates the formation of colloidal vesicles rich in free fatty acids and glycerides, which may further retain drug molecules in the solubilised state prior to absorption [4]. In doing so, absorption across the intestinal epithelium increases significantly for highly permeable Biopharmaceutics Classification System (BCS) Class II drug molecules when formulated as LBDDS.

The physicochemical properties and pharmacokinetic performances of LBDDS vary significantly depending on the composition, concentration and solubilisation mechanism of lipid excipients. Of specific interest to this review are self-emulsifying drug delivery systems (SEDDS) due to their commercial potential, versatility and capacity to vastly improve the pharmacokinetic profiles of poorly water-soluble drugs. SEDDS are typically composed of an isotropic mixture of lipids, surfactants and (optionally) co-surfactants and co-solvents, that form fine lipid-in-water emulsions upon dispersion and mild agitation within the GI tract [5]. In this review, the designation of the term SEDDS will refer to the complete subdivision of SEDDS; including self-microemulsifying drug delivery systems (SMEDDS) and self-nanoemulsifying drug delivery systems (SNEDDS). The emulsification of lipids within the GI tract facilitates improved drug dissolution, by increasing the interfacial surface area

available for drug release and absorption [6, 7]. In addition, specific self-emulsifying lipids and excipients promote drug permeability across the intestinal epithelium, as well as lymphatic transport of drugs into the systemic circulation [8].

Despite the ability of SEDDS to improve the oral absorption of hydrophobic drugs, their commercial success has been mostly limited to date [9]. Of the SEDDS currently marketed, the majority are composed of liquid formulations filled into either soft gelatine (Sandimmune Neoral[®], Norvir[®], Rocaltrol[®], Convulex[®]) and hard gelatine capsules (Lipirex[®], Gengraf[®]) [10]. The inability for the commercial success of SEDDS to fully reflect their therapeutic potential has been attributed to a number of factors, including limited stability and portability of liquid-SEDDS formulations, propensity for drug crystallisation and precipitation *in vivo*, low drug loading, poor *in vitro-in vivo* correlations (IVIVC) and costly manufacturing and distribution processes [11-14]. A common approach used to overcome these fundamental drawbacks is to transform liquid-SEDDS into solid dosage forms that impart physicochemical stability and reduce production costs while retaining, or optimising, the pharmacokinetic benefits associated with lipids. An array of solidification approaches can be utilised to develop solid-SEDDS, which can be categorised into those that; (i) emulsify *in vivo*, and (ii) are pre-emulsified and stabilised *in vitro*, allowing for emulsion redispersion within the GI tract. In doing so, a number of biopharmaceutical advantages can be imparted to the SEDDS formulation by solidification (Figure 1), including:

- (i) *prolonged gastric residence*: the time taken for gastric emptying and overall transit can be extended by solidifying liquid-SEDDS with various polymers, such as HPMC and microcrystalline cellulose, that exhibit favourable interactions with stomach epithelial cells [15, 16] or by incorporating floating excipients that enable

the formulation to remain buoyant within the gastric media. In doing so, the overall dissolution time and the time available for absorption is extended [17].

- (ii) *improved intestinal solubility*: solidification of SEDDS can impart improved intestinal solubility through a number of mechanisms, including stabilising supersaturated drug states and modulating lipolysis of digestible lipids. For example, polymeric nanoparticles can be used as polymeric precipitator inhibitors (PPIs) that retain solubilised drug molecules in their supersaturated state in the small intestine [18], while also altering the activity of digestive enzymes, through changes in nanostructure and surface chemistry of the solid carrier material, to control the rate and extent of release of lipid digestion products. In doing so, the precipitation inhibition effect and solubilising mechanism of lipolysis products improve the intestinal solubility of encapsulated drug molecules [19, 20].
- (iii) *improved drug permeability*: SEDDS can be formulated with known solid-state intestinal permeation enhancers, such as chitosan and mucoadhesive polymers [21, 22] to promote drug permeability across the intestinal epithelium. While little work has focused on forming solid-SEDDS for permeability enhancement, two studies by Kanuganti *et al.* [23] and Sermkaew *et al.* [24] have presented the ability to optimise intestinal drug permeation by combining liquid-SEDDS excipients with various silicates, which has highlighted the potential for solid-SEDDS to be used as delivery vehicles of BCS Class IV drug compounds.

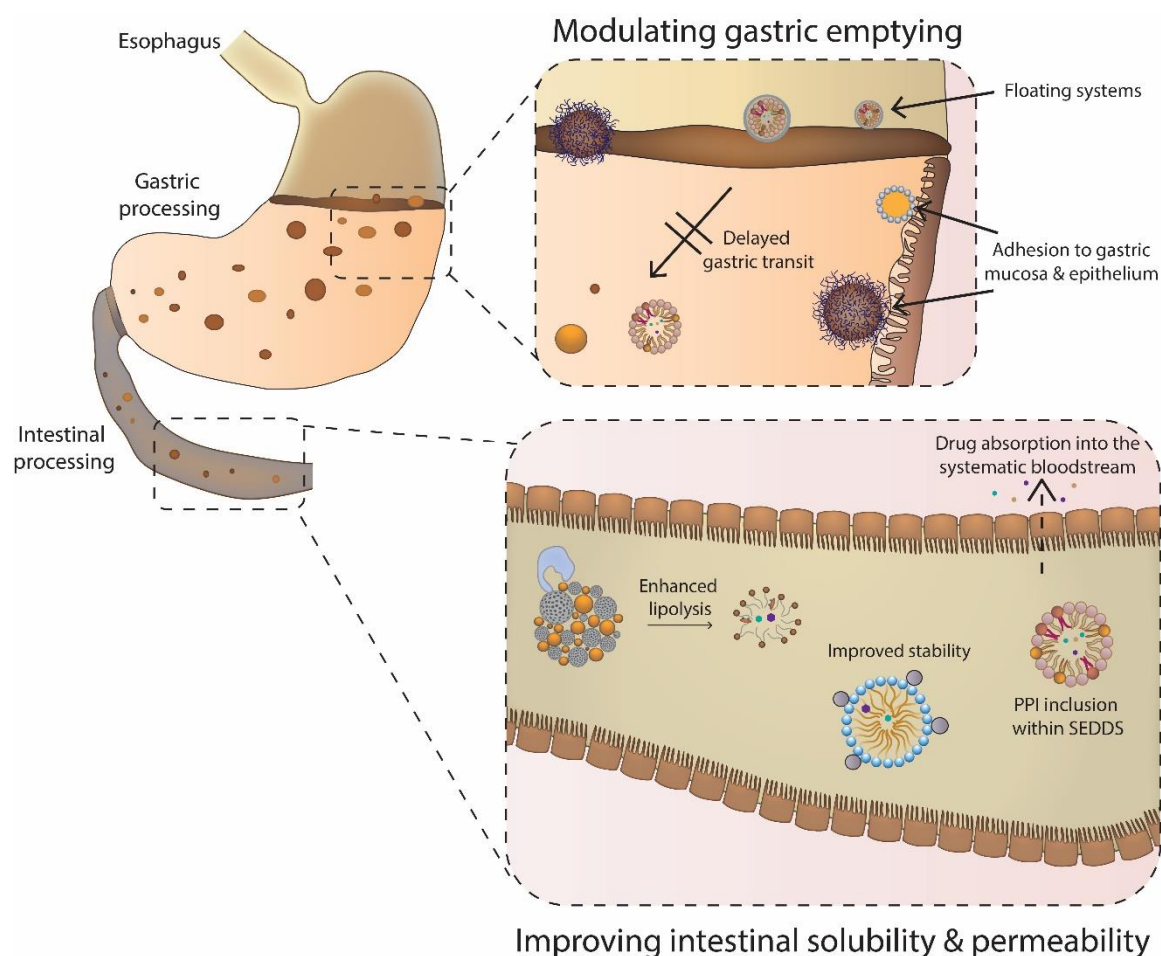


Figure 1: Schematic representation of the potential biopharmaceutical benefits associated with solid-self-emulsifying drug delivery systems (solid-SEDDS), including extending gastric emptying and enhancing intestinal solubilisation by manipulating lipase-mediated hydrolysis and incorporating polymeric precipitation inhibitors (PPIs).

The aim of this review is to elucidate and discuss the recent progress that has been made in designing and developing novel solid-SEDDS, while presenting opportunities and challenges that must be addressed to translate promising pre-clinical and clinical research into commercially viable drug formulations. Specific emphasis is placed on solidification design considerations that can influence the final physicochemical and biopharmaceutical performance of solid-SEDDS. This review primarily focuses on the transformation of liquid-

SEDDS into solid dosage forms that are composed of nanostructured hybrid systems, which subsequently exist as free-flowing and compressible powders. The insights derived from the development of innovative solid-SEDDS systems have important implications for harnessing the full therapeutic potential of poorly water-soluble drug compounds, as well as the future design of next generation lipid-based drug delivery vehicles.

2. Rationale for Transforming Liquid-SEDDS into Solid Dosage

Forms

Solidification of SEDDS affords a multitude of benefits compared to precursor liquid-SEDDS, which can be summarised within the following categorical advantages; (i) improved drug solubilisation and dissolution, (ii) improved safety, (iii) controlled drug release, and (iv) industrial and commercial benefits (Figure 2). The following section highlights the various perspectives for converting liquid-SEDDS into solid dosage forms, specifically those that exist as free-flowing and compressible powders. Emphasis is placed on the biopharmaceutical performance of solid-state formulations with respect to their liquid lipid precursors, to highlight potential for use as oral delivery vehicles for challenging hydrophobic compounds.



Figure 2: Rationale for transforming liquid-SEDDS into solid dosage forms.

2.1 Improved Solubilisation and Dissolution

Drug crystallisation and precipitation, after emulsification in the GI tract, are predicted to be the primary factors contributing to variable and unpredictable *in vivo* pharmacokinetics associated with conventional SEDDS [25]. Subsequently, low drug loading is recommended within liquid-SEDDS [26], since loading is controlled by the drug saturation solubility within the liquid lipid phase and should take into consideration the drug solubility during and after emulsification. Low drug loading is considered a key limitation for formulations of high dose BCS Class II and IV drugs, which has triggered recent advances in formulation technology to attribute focus to the fabrication of supersaturated SEDDS (super-SEDDS). In super-SEDDS, drug molecules are either (i) encapsulated within the lipid phase at a concentration above their equilibrium solubility [27-29] or (ii) formulated with excipients that generate

supersaturated drug solutions when dispersed in GI media [18, 29-32]. One approach to successfully fabricate super-SEDDS is to combine liquid self-emulsifying lipids with solid carrier materials, including porous colloids and PPIs. Various strategies have been successfully employed to fabricate solid-state super-SEDDS, with promising physicochemical and biopharmaceutical outcomes. These include:

- (i) *Pre-loading porous carrier materials with lipophilic drugs prior to combining with liquid-SEDDS excipients.* Poorly water-soluble drug nucleation and crystallisation is restricted when adsorbed in mesoporous materials, through spatial confinement, and therefore, the drug is retained in its molecularly dispersed/dissolved form [33]. A synergistic effect is achieved when self-emulsifying lipids are co-encapsulated within a porous material, since the lipids facilitate solubilisation during GI processing and drug diffusion [34-37]. Rao *et al.* [34] investigated the role of combining porous silica particles with self-emulsifying lipids in enhancing the drug loading of lovastatin. It was determined that pre-loading mesoporous silica with molecularly dispersed lovastatin from organic solvent, prior to forming hybrid structures with self-emulsifying lipids, facilitated a 3-fold improvement in drug encapsulation, compared to the precursor liquid-SEDDS formulation. The super-SEDDS formulation retained lovastatin within a solubilised state during *in vitro* intestinal lipolysis studies and enhanced oral bioavailability of lovastatin 2.8-fold compared to crystalline drug. Further, *in vivo* pharmacokinetic studies highlighted a relationship between silica porosity and bioavailability, with an increase in silica specific surface area correlating to an increase in lovastatin bioavailability [34].

- (ii) *Stabilising supersaturated lipid phases with solid carriers.* A number of techniques exist to encapsulate hydrophobic compounds within emulsified lipids at concentrations above their equilibrium solubility, including pH adjustment (limited to ionisable drugs) [38, 39] and subjecting lipids to heating and cooling cycles [40]. However, the thermodynamic instability associated with excess solute contained within the lipid phase triggers crystallisation upon changes in environmental conditions or during storage. Porous silica has been successfully employed to stabilise the supersaturated lipid phase, as exemplified by two recent case studies. Firstly, the water- and lipid-resistant weak base, albendazole, was supersaturated within dispersed lipid droplets via a pH adjustment method [29]. Secondly, ibuprofen was loaded within lipid at concentrations 4-fold greater than its equilibrium solubility, by heating the lipid solution at temperatures of up to 60°C [28]. In both scenarios, the supersaturated lipid was confined within porous silica matrices, resulting in super-SEDDS that spontaneously redispersed into submicron emulsion droplets and silica particles upon dilution within GI media. For both drug molecules, the porous silica matrix enabled drug molecules to be loaded within the SEDDS preconcentrate at a supersaturated concentration, which was retained during *in vitro* assessments. In doing so, this triggered enhancements in *in vivo* pharmacokinetics in comparison to the non-supersaturated formulations. It is important to note, that long-term stability studies are required to fully validate the ability for supersaturated solid-SEDDS to retain supersaturated drug molecules in their solubilised state during storage.
- (iii) *Combining solid carriers with precipitation inhibitors and SEDDS excipients.* An alternative form of multifunctional solid excipients that can be combined with lipids

for a synergistic effect are PPIs, such as Pluronics [18], cellulose derivatives [41], and polymeric nanoparticles (e.g. poly(lactic-co-glycolic) acid (PLGA) nanoparticles) [19]. PPIs stabilise the metastable saturated and supersaturated states of a wide range of lipophilic drugs when encapsulated within LBDDS [18]. Hydrogen bonding and/or hydrophobic interactions between drug molecules and polymers may increase the nucleation activation energy, leading to delayed crystal nucleation and growth [42]. This phenomenon is especially important for poorly soluble weak base drugs that exhibit pH-dependent solubility due to protonation in acidic environments. The ionisation of such compounds leads to drug supersaturation within the gastric environment, with drug solubility rapidly decreasing as the drug transits towards neutral conditions of the small intestine. Thus, the predisposition to intestinal precipitation significantly restricts the rate and extent of oral absorption. Subsequently, the efficacy of conventional SEDDS and LBDDS in delivering weak bases has been shown to be limited due to their inability to overcome equilibrium solubility discrepancies within the gastrointestinal tract [43]. However, multiple studies have demonstrated synergistic effects between solid PPIs and self-emulsifying agents in overcoming pH-provoked precipitation of poorly water-soluble weak bases [18, 20, 44-50]. Hydrophobic interactions between drug and PPIs restricts the conversion of the supersaturated drug molecule to the more thermodynamically stable crystalline state upon gastric emptying, allowing for increased drug loading within the formulation and facilitating a greater extent of drug dissolution upon reaching the primary site of absorption [37].

2.2 *Controlled Drug Release & Delivery*

2.2.1. Multicomponent Release

The synthesis of solid-SEDDS affords the potential to deliver drug compounds through multiple release mechanisms. This has important implications for the delivery of poorly water-soluble drugs, since such formulations ideally possess slow release kinetics to (i) prevent drug release during gastric transit, and (ii) sustain drug solubilisation throughout the GI tract (Figure 1) [51]. Drug release from emulsified lipids upon dilution in aqueous media is typically fast and diffusion- or digestion-dependent [52]. This can be regulated by varying emulsion droplet size, fatty acid chain length and digestibility of lipids, but finely regulating release kinetics from emulsified lipids has proven challenging [53]. In contrast, drug release from solid carriers is typically matrix- or erosion-dependent, which presents the ability to precisely fine-tune drug release kinetics based on various material characteristics [54].

This phenomenon was recently demonstrated by spray drying dispersed SEDDS stabilised by PLGA nanoparticles for the delivery of the model poorly water-soluble weak base drug, cinnarizine [20]. Cinnarizine was loaded within both the lipid and polymer phase in this spray dried solid-state hybrid formulation, resulting in dual release kinetics. That is, drug release during *in vitro* gastric dissolution was initially rapid, due to diffusion from the lipid droplets, followed by a slow secondary release phase from the polymeric nanoparticles. Furthermore, by stabilising lipid droplets within a nanostructured network, *in vitro* lipolysis kinetics were enhanced >2.5-fold compared to a submicron emulsion. By controlling cinnarizine release and lipolysis kinetics through this co-encapsulation approach, a >2.5-fold reduction in pH-provoked precipitation was observed [20], which translated to a >2-fold enhancement in the area under the curve (AUC) following oral administration to rats, compared to two alternate LBDDS [44].

2.2.2. *Site-Specific Release*

The solidification of SEDDS introduces the ability for controlled and targeted release of encapsulated drug cargo by selecting suitable solid carriers that are responsive to changes in local environment. While this can also be achieved with liquid-SEDDS, the improved physicochemical stability of solid-SEDDS presents a more feasible approach to controlled release of drug compounds [55-57]. The most commonly employed approach is to encapsulate SEDDS within pH-responsive excipients, such as polymers [58, 59] and functionalised porous silica particles [60]. This strategy is of specific interest for the oral delivery of pH- and enzyme-sensitive macromolecules, such as proteins, peptides and nucleic acids. Toorisaka *et al.* [61, 62] recently harnessed this approach by confining insulin and emulsified lipids within a pH-responsive polymer shell via lyophilisation to restrict drug leakage during gastric dissolution and act as an enteric-coated SEDDS. In doing so, insulin was effectively protected from pH- and enzyme-mediated degradation within the gastric environment. The change in acidity during gastric emptying subsequently triggered the collapse of the polymeric shell and emulsification of insulin-loaded lipid droplets, facilitating greater oral absorption across the intestinal epithelium [61].

2.3 *Improved Safety*

2.3.1. *Reduced Relative Surfactant Concentrations*

Since it is desirable to create micro/nano-sized emulsion droplets and micelles to increase the surface area to volume ratio, and thus increase lipase-mediated hydrolysis, high surfactant concentrations must be employed to sufficiently stabilise the high surface area lipid-in-water interface and ensure the drug remains in the dissolved state during storage and upon

administration [63, 64]. Subsequently, SEDDS formulations inherently contain large concentrations of surfactants (typically >30% w/w). While this serves as an effective means to overcome limitations associated with drug crystallisation and precipitation of poorly water-soluble compounds, studies have demonstrated that high doses of surfactants can be poorly tolerated during chronic use [25]. However, stabilising the emulsification process with biocompatible [65] and/or biodegradable solid excipients [54], has demonstrated the ability to provide an equivalent or enhanced pharmacokinetic performance of SEDDS formulations at reduced surfactant dosing. This was demonstrated by Gao *et al.* [66, 67] whereby lower surfactant concentrations were used in combination with a solid PPI to reduce surfactant-mediated side effects and rapid absorption of multiple poorly water-soluble drugs. In the liquid-SEDDS, the surfactant levels alone were too low to achieve adequate micellar/emulsion formation in order to solubilise the entire drug load. However, when combined with the HPMC, the drug compounds were sufficiently solubilised to allow for complete dissolution. In reducing surfactant concentration, the safety and toxicity concerns of conventional SEDDS can be overcome by replacing a significant proportion of surfactant content with solid stabilisers. The authors recommend employing Generally Recognised as Safe (GRAS) listed pharmaceutical- and food-grade excipients approved by the FDA, for the solidification of SEDDS to avoid toxicity concerns associated with other potential solid excipient candidates [68].

2.3.2. *Improved Oxidative Stability*

SEDDS lipid excipients typically remain chemically stable when they are maintained in the original sealed packaging under recommended conditions of storage [9]. However, lipids and oils become prone to degradation through lipid peroxidation when exposed to air, light, water

moisture, changes in pH and heat [69]. The release of hydroperoxides and other volatile by-products have a detrimental influence on SEDDS by; (i) reducing the physicochemical stability of the liquid-SEDDS [70, 71], (ii) chemically degrading encapsulated drug compounds [72, 73], and (iii) increasing the *in vivo* toxicity of the formulation [74].

Due to the harmful and undesirable side effects associated with lipid peroxidation, it is fundamental to preserve and protect all lipid excipients within SEDDS. Emerging studies performed by functional food scientists and engineers have shown the ability to prevent lipid degradation within LBDDS by transforming the liquid-LBDDS into a solid-state LBDDS [75-77]. Lipid oxidation kinetics are greatest at the lipid-in-water or lipid-in-air interface [78-81]. Thus, physically shielding lipids from the water and air interfaces, by encapsulating lipids within solid-state matrices, restricts the rate and extent of lipid decomposition and therefore, preserves the integrity of the confined lipid species [82-86]. This has been achieved with various solid excipients, including proteins, such as caseins and soy protein [87-89], carbohydrates, including cellulose, starch and xanthan gum [90-92], and chemically inert colloids, such as silica and graphene oxide [93-97]. While much of this work has been performed to maintain the integrity of complex food-grade lipids, it is hypothesised that incorporating equivalent formulation design within SEDDS will impart physical and chemical stability, due to the reduced susceptibility for lipid oxidation in solid-SEDDS.

2.4 Additional Industrial Perspectives

From an industrial perspective, a number of considerations need to be built into the development of a new formulation irrespective of the dosage form and administration route. A patient centric design is normally used (*i.e.* what, from a patient perspective, would be a suitable dosage form and administration frequency? What would be a convenient packaging

setting?). For example, administering a liquid solution orally can be associated with an unpleasant taste, which may be relevant for paediatric patients. This may be circumvented by adsorbing the liquid excipients onto a solid carrier, producing a formulation that is easy to administer to children [98, 99]. Besides these very visible factors, other elements such as chemical and physical stability at ambient temperature may be important both for logistical reasons, but also for the benefit of the patient that hereby may avoid special storage conditions.

Additionally, elements of packaging design, industrial processing, scalability, quality, ease of manufacturing, and the associated cost of goods are important. When lipids are solidified there is the possibility of producing a range of dosage forms, *e.g.* sachets, powder filled capsules, and tablets. These dosage forms can be produced on standard pharmaceutical processing equipment making the supply chain simpler and thereby cheaper. Further, solidification prevents direct contact between the LBDDS and the capsule, which may improve the compatibility and thereby enable improved industrial production [100]. Solidification of SEDDS can support the above factors in some cases and could therefore be applicable to development projects.

3. Design Considerations for the Development of Solid-SEDDS

Transforming liquid-SEDDS into solid dosage forms affords the ability to distinctly change and modulate the physicochemical properties and pharmacokinetic performance of encapsulated lipophilic drugs. Subsequently, considerable formulation design is required to obtain the desired biopharmaceutical performance of solid-SEDDS. This section highlights fundamental considerations that should be made when fabricating solid-SEDDS, including selecting the most applicable solidification approaches and excipients for the therapeutic

compound of interest. Critical analysis will be provided on the influence of material characteristics and interactions on the oral bioavailability of lipophilic compounds.

3.1 Solidification Approach

Different solidification techniques impart unique changes to the physicochemical properties *in vivo* performance of the SEDDS. Table 1 has been designed to aid researchers in selecting an appropriate technique to fabricate solid-SEDDS with desired properties for optimal biopharmaceutical performance. This section reviews each critical consideration required for selecting the most appropriate solidification approach, with respect to the form of precursor lipids, desired dosage form and drug loading, thermal stability of the formulation/therapeutic and potential interference on emulsification mechanisms.

Table 1: Considerations when selecting a technique to solidify SEDDS.

Technique	Key concept/ process	Primary approach		Form of precursor liquid- SEDDS		Physical form of resulting product	Possible thermal stability issues?	Max. reported drug load (% w/w) [9]	Max. reported lipid load (% w/w) [9]	Best suited for what drug dose/ potency?	Rate of self- emulsification upon oral administration	Control over solidification conditions	References
		To simply solidify	To induce change in performance	Excipients	Pre-emulsified lipids								
Physical adsorption to solid carriers	Adsorption of SEDDS to the solid carrier via mixing with a blender.	X	X	X	X	Powder or granules		10	80	Low dose, high potency	++	+	[28, 101-103]
Hot/melt granulation/extrusion	High shear mixing of SEDDS and a solid carrier. Followed by optional forcing through a die.	X		X		Granules (agglomerates) which can be extruded into pellets of different shapes and sizes	X (during high shear mixing and if using molten SEDDS)	80	50	Low-medium dose	++	++	[104-108]
Freeze drying	Sublimation of the aqueous phase from frozen SEDDS stabilised by a carrier material.	X	X	X	X	Powder or granules (porous agglomerates)	X (<0°C to freeze, consider using a cryoprotectant)	50	60	Low dose, high potency	+++	++	[109-112]
Spray drying	Evaporation of solvent from atomized spray of SEDDS (stabilised by a solid material) at high temperature.	X	X	X	X	Powder or granules (porous and spherical particles)	X (short exposure to high temperature - max 220 °C)	50	60	Low dose, high potency	+++	+++	[20, 113-120]

3.1.1. Form of precursor lipids

The primary approach for solidification of liquid-SEDDS is dependent on the form of the precursor SEDDS and can be classified into the following two categories which have been schematically illustrated in **Error! Reference source not found.**:

- (i) *Solidification of liquid-SEDDS excipients which self-emulsify in vivo.* The primary objective of this solidification approach is to produce a solid dosage form that retains the GI self-emulsification properties of the encapsulated lipids [121, 122]. The most commonly employed techniques to achieve this are adsorption onto a porous solid carrier and melt/granular extrusion using a polymeric solid carrier [12]. Since the aim is not necessarily to enhance the pharmacokinetic properties of the formulation, it is important to consider the impact of solidification on the solubilisation capacity and dissolution mechanism of the formulation. A multitude of studies have demonstrated reduced *in vitro* dissolution [123, 124] and oral bioavailability [125, 126] of drugs when formulated as solid-SEDDS compared to their precursor liquid-SEDDS counterpart. This suggests more extensive design considerations are required when solidifying liquid-SEDDS to maintain or enhance *in vivo* drug absorption.
- (ii) *In vitro stabilisation of dispersed SEDDS that spontaneously re-emulsify in vivo.* The solidification of pre-dispersed emulsions presents an alternate way of delivering SEDDS orally. Solidifying dispersed liquid-SEDDS offers the ability to finely tune the physicochemical and solubilisation properties of the formulation, through intelligent material design. The solidification of dispersed SEDDS stabilized with a solid carrier, typically in the form of Pickering emulsions, via

either spray drying or freeze drying, produces particles with complex internal nanostructures which impart improved *in vivo* oral drug delivery performance compared to the liquid precursor emulsion. The performance is improved through rapid re-emulsification, rapid digestion, controlled release and specific solid carrier interactions [127]. Freeze drying and spray drying are the two key techniques used to solidify Pickering emulsions and have been directly compared in two studies [109, 110]. Singh *et al.* [110] compared the influence of freeze dried and spray dried solid-SEDDS on the *in vitro* dissolution and *in vivo* oral bioavailability of valsartan. The spray dried SEDDS exhibited superior characteristics in terms of particle size uniformity, particle flow properties and rapid GI processing, as well as minor improvements in pharmacokinetic performance (~5% higher oral bioavailability), which indicates the importance of selecting the most appropriate dehydration method for stabilization of emulsified lipids.

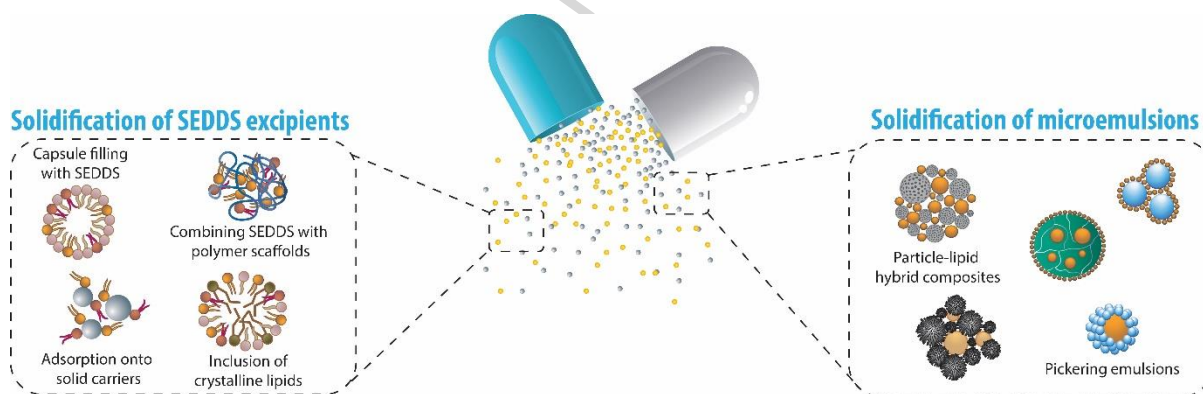


Figure 3: The two approaches to solidify liquid-SEDDS, (i) solidification of liquid-SEDDS excipients, or (ii) stabilisation of dispersed emulsions/micellar systems.

3.1.2. Solid Dosage Form

Solid-SEDDS in the form of powders or granules are appealing as they are generally compatible with pre-existing tableting or capsule filling procedures and equipment [128]. The pre-requisite for solid-SEDDS powders and granules to be compressed into tablets and filled into capsules is flowability [129]. Free-flowing powders can be achieved through careful selection of a solid carrier/tableting excipient or through subsequent granulation of the powder with a binder [12]. Powders are typically fabricated utilising physical adsorption onto carriers, freeze drying or spray drying, whereas granules are fabricated using hot/melt granulation. Granules can be further modified to form solid-SEDDS pellets with desired shapes and sizes through the use of extrusion and spheronisation [130]. If desired, these pellets can be subsequently coated with polymeric or enteric coatings to impart specific release properties.

3.1.3. *Thermal Stability of Therapeutic Molecules and Lipid Excipients*

The thermal stability of SEDDS excipients is vital for solidification techniques which involve heating or cooling of the formulations. Elevated temperatures can cause the degradation of active ingredients and oxidation of lipids, resulting in inefficient drug loading and undesirable degradation products [131]. In addition, the thermal stress induced by freezing can destabilise SEDDS formulations, resulting in particle aggregation and poor re-dispersibility [132]. Such effects have been observed during hot melt extrusion [133, 134] and freeze drying of SEDDS formulations [109].

Surasarang *et al.* [134] observed that up to 97% of albendazole was degraded when attempting to fabricate an amorphous solid dispersion using hot melt extrusion, compared to no degradation when using spray drying. Degradation occurred during extrusion due to heat exposure and shear stress over a longer residence time (13 min). No degradation occurred

during spray drying, as the time in which the drug is exposed to high temperatures was very short and reduced the risk of thermal degradation. In addition, heat accelerates the oxidation of some lipid excipients, which can be minimised by the use of saturated fatty acids or the use of antioxidants [135]. To avoid thermal degradation of active ingredients during solidification, the required temperature, residence time and thermal stability of the excipients must be considered when selecting a suitable solidification method.

Bamba *et al.* [136] reported the de-stabilising effect of the freeze/thaw process on nanoemulsions, resulting in significant coalescence of the emulsion droplets. A slower cooling rate and the use of a cryoprotectant was found to mitigate the de-stabilising stresses induced by freezing. Yasmin *et al.* [37] demonstrated the benefits of cryoprotectants for the solidification of liquid-SEDDS by freeze drying, for preventing irreversible aggregation and allowing re-dispersion in water. For these reasons, cryoprotectants are used extensively in the freeze drying of SEDDS [111, 112].

3.1.4. *Drug and Lipid Loading Implications on the Required Dosage*

The required dose of a drug compound is one of the major limiting factors to the use of solid-SEDDS. Typical drug loading levels of less than 10% w/w are achieved for SEDDS, which is dictated by the solubility of the drug in SEDDS [137]. Consequently, it is essential to select a solidification approach that retains maximum drug loading within the solid-SEDDS formulation, in its dissolved form. The inclusion of additional solid excipients to solidify SEDDS further dilutes the drug load, limiting solid-SEDDS to highly potent and low dose drug molecules (*e.g.* <10 mg dose) [138]. Yasmin *et al.* [109] compared freeze drying and spray drying methods for the model drug, celecoxib, when solidifying dispersed SEDDS stabilized by porous silica particles [35, 139]. Both drying methods resulted in porous, free-

flowing powders; however, only the freeze-dried formulation possessed a 100% lipid encapsulation efficiency, which translated to higher drug loading compared to the spray dried solid-SEDDS.

3.2 Solidification Excipients

The selection of carrier excipients for the solidification of SEDDS has fundamental implications for the resulting physicochemical properties and pharmacokinetic performance of the formulation. Consequently, care should be taken when choosing an appropriate excipient for the therapeutic of interest. A multitude of solid carrier excipients have demonstrated the potential to be successfully combined with SEDDS to improve the pharmacokinetic performance of lipophilic drugs. The most commonly employed categories of excipients and their associated advantages and disadvantages are shown in Figure 4. Previous reviews have extensively introduced the properties of these excipients [1, 127], and therefore, this will not be the focus here. Rather, emphasis will be placed on providing an in-depth analysis of the influence of solid carrier properties on their interactions with lipid molecules, with reference to how this impacts drug solubilisation and absorption.

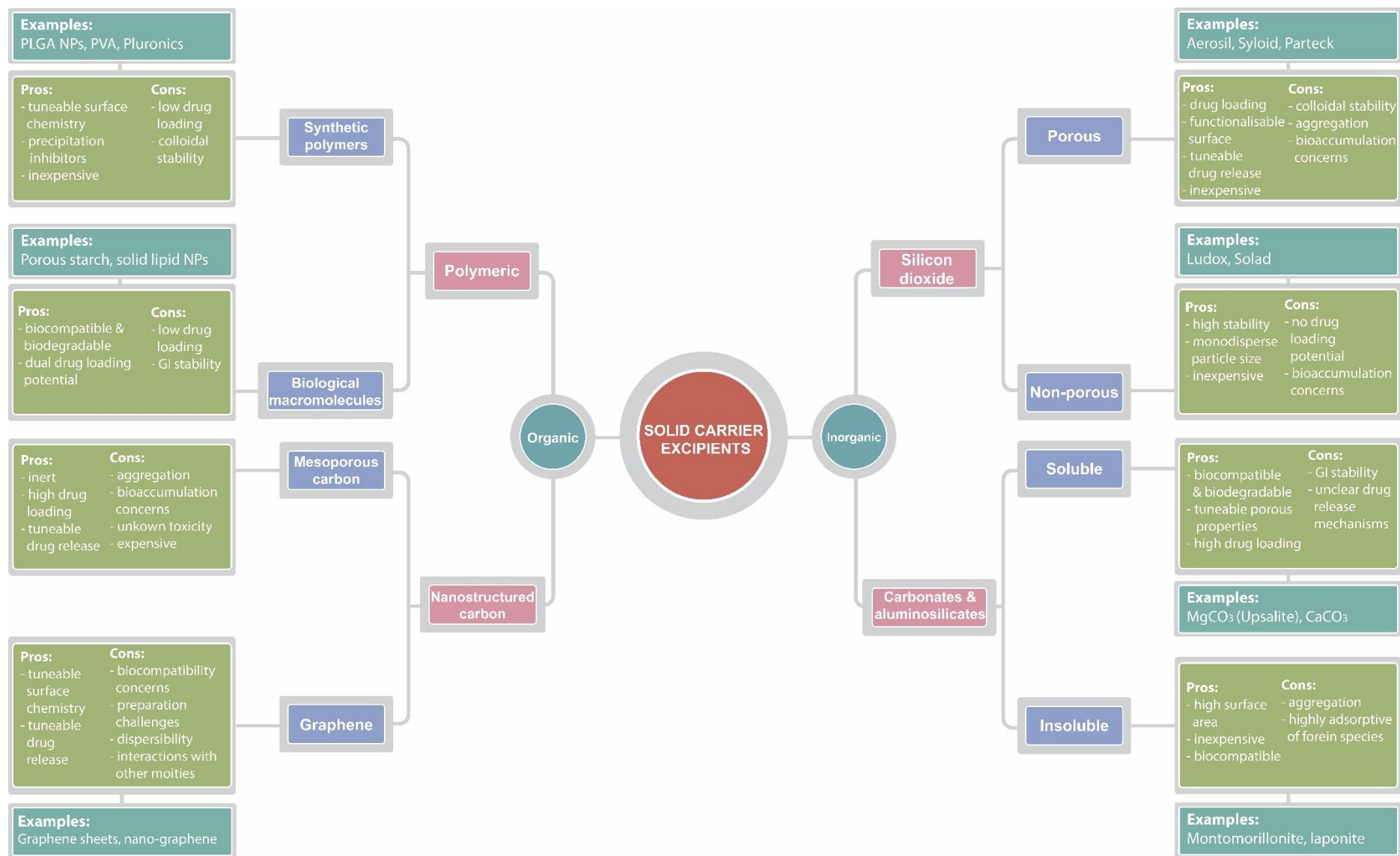


Figure 4: Categorical overview of the various solid carrier excipients applicable for solidification of SEDDS, with corresponding advantages and limitations. Abbreviations: GI: gastrointestinal; NPs: nanoparticles; PLGA: poly(lactic-co-glycolic) acid; PVA: polyvinyl alcohol.

3.2.1. *Influence of Lipid-Solid Carrier Interactions on Lipid Digestion*

Lipid hydrolysis is a fundamental *in vivo* process that has the potential to exert a positive or negative effect on the GI solubilisation of lipophilic drugs confined within digestible lipids, depending on the saturation solubilities of the drug molecules within the various lipid species [140]. The processing of lipids is initiated within the stomach, where digestive enzymes hydrolyse the ester group of glycerides to form free fatty acids and monoglycerides [141]. Gastric and pancreatic lipases, the primary digestive enzymes, are surface active enzymes that require an interface to undergo a conformational change into their active form [142]. This occurs due to the presence a polypeptide loop that protects the mostly hydrophobic active site from the aqueous environment, until weak adsorption onto a liquid-in-liquid or solid-in-liquid interface triggers this lid domain to open, exposing the catalytic domains [143]. The interfacial activation mechanism establishes the potential to modulate lipase activity through colloidal and interfacial engineering of the lipid-in-water interface [144, 145]. A proven approach to alter the bioaccessibility of lipid to digestive enzymes, is to formulate lipids with solid carriers with varying surface chemistry and nanostructure [146, 147].

Solid carrier excipients manipulate GI lipolysis via three main mechanisms (Figure 5);

- (i) *Modulation of the lipid-in-water interfacial surface area.* Since lipid digestion is an interfacial process, varying the surface area accessible to lipase enzymes triggers a change in lipid digestion kinetics. Adsorption of liquid-SEDDS excipients onto porous solid carriers can significantly manipulate the interfacial surface area of lipid, compared to conventional emulsion droplets. This has been shown extensively by confining digestible triglycerides within mesoporous silica particles [145-151], whereby the lipid-in-water interfacial area is relative to the lipid loading and relative porosity of the particles. A 4.5-fold improvement in lipolysis kinetics was observed when medium chain triglycerides were encapsulated within hydrophilic porous silica particles compared to a submicron emulsion, due to a 5.1-fold increase in interfacial surface area [146]. In doing so, this triggered a substantial increase in rate and extent of lipid colloidal phases formed within the aqueous environment [149]. However, when colloidal particles have been utilised to stabilise emulsified lipids, an interference effect has been observed, since the particle stabilisers physically shield the lipid-in-water interface from digestive enzymes [19]. Tan *et al.* [150] investigated the susceptibility for porous silica nanoparticles to inhibit lipase activity when partially stabilising lipid phases at various concentrations. It was determined that porous silica particles acted as a competitive lipase inhibitor when co-dosed with SEDDS excipients, since the particles weakly adsorb to the lipid-in-water interface and thus, sterically hinder lipases ability to access the lipid substrate. This is in contrary to the mechanism of enhancement observed for porous silica particles when a three-dimensional hybrid matrix structure is formed. Alternate particles that have shown to restrict lipase

bioaccessibility when used as stabilisers include polymeric nanoparticles [19, 152], clay platelets [153] and carbohydrate nanocrystals [154-160].

(ii) *Provision of a solid-in-water interface for interfacial activation/deactivation.*

Encapsulating lipid species within solid excipients introduces the ability for lipase to adsorb to bare solid surfaces and thus, the solid carrier acts as a substrate-enzyme immobilisation support. The surface chemistry of the solid carrier controls the orientation and conformation of enzyme molecules, which can exert a positive or negative effect on lipase activity [161]. This was recently probed by utilising time-of-flight secondary-ion mass spectrometry (ToF-SIMS) to distinguish the orientation of lipase at various silica surfaces [162]. It was found that hydrophilic silica surfaces weakly adsorb pancreatic lipase molecules in their active conformation, whereas lipase adsorbs more extensively to hydrophobic surfaces restricting conformational changes and the opening of the lid domain protecting the active site. This correlated strongly to *in vitro* lipolysis findings, whereby a >3-fold enhancement in lipase activity was observed when digestible lipids were adsorbed into hydrophilic porous silica, compared to hydrophobic silica [163].

(iii) *Triggering the release/retention of lipid digestion species.* Lipid digestion species, specifically fatty acids and monoglycerides, are surface-active products that adsorb to the lipid-in-water interface due to their amphiphilic nature [164-166]. Consequently, lipase reactions are considered a self-limiting processes, as lipase-mediated hydrolysis products ‘poison’ the substrate interface leading to a reduction in lipid bioaccessibility and digestion kinetics [164, 165]. Solid carriers can manipulate this self-limiting process by controlling the rate and extent of lipolysis

product partitioning towards the aqueous phase through electrostatic and agglomeration interactions [144]. This was highlighted recently by comparing hybrid particles composed of submicron lipid droplets and either negatively- or positively-charged PLGA nanoparticles [19]. Lipid hydrolysis kinetics were 2-fold greater for hybrid particles composed of negatively-charged PLGA nanoparticles, compared to positively-charged particles, due to the electrostatic repulsion present between the particle surface and fatty acids. This interaction facilitated the prompt expulsion of fatty acids into the aqueous phase, and thus, reduced the interference of digestion products at the lipid-in-water interface. In contrast, an electrostatic attraction was apparent between positively-charged PLGA nanoparticles and fatty acids, leading to their retention within the solid phase and interference with lipase action. This reduction in aqueous phase partitioning of lipid digestion products has been shown to correlate with a reduction in aqueous solubilisation for the model drug, coumarin 102, when formulated with a range of solid-SEDDS [167].

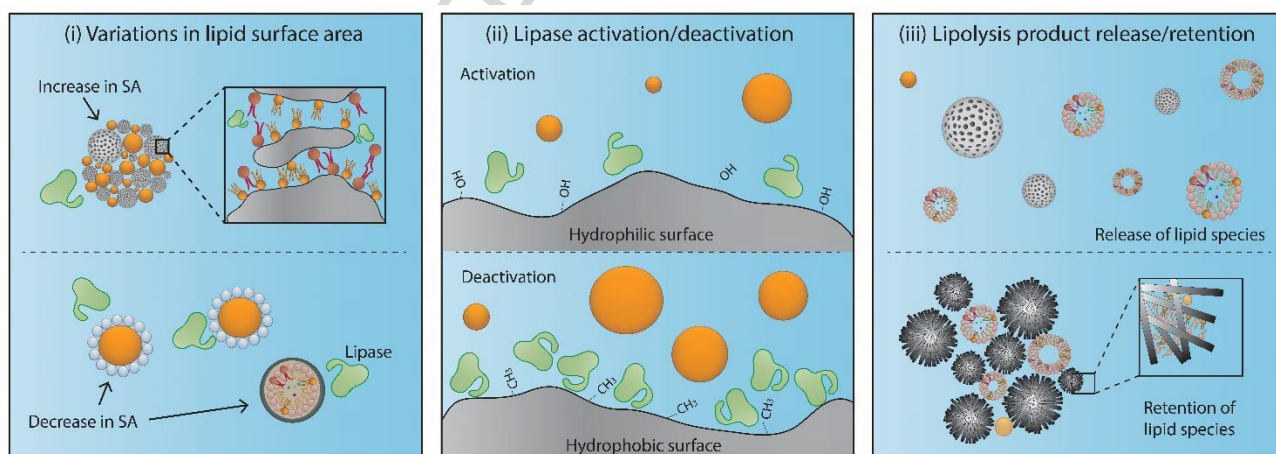


Figure 5: Schematic representation of the mechanisms for controlling gastrointestinal lipolysis through colloidal engineering with solid excipients. Lipase-mediated digestion can be controlled by (i) manipulating the surface area (SA) of the lipid-in-water interface and

thereby, altering the bioaccessibility of lipid [146]; (ii) orientating lipase molecules on surfaces for optimal activity [162]; and (iii) triggering the release or retention of lipid digestion products through electrostatic interactions with the solid carrier [149, 167].

By forming solid-SEDDS it is possible to finely tune the digestibility of lipids, which can correspond to a change in the oral bioavailability of encapsulated drug molecules. It is important to note that conventional *in vitro* lipolysis protocols overlook intragastric lipolysis and only mimic the intestinal phase of digestion, despite gastric processing accounting for ~5-30% *in vivo* lipolysis [168, 169]. Furthermore, gastric lipase exhibits significantly different interfacial activity compared to pancreatic lipase and exposure to gastric conditions and transport can facilitate considerable changes to solid-SEDDS structure, surface chemistry and stability, which can subsequently (i) alter the lipid:solid carrier microenvironment and interaction with pancreatic lipase [170-174], (ii) activate pancreatic lipase [175, 176], and (iii) alter the solubilisation of poorly water soluble drugs [168, 177]. Consequently, the authors propose that future studies assessing *in vitro* performance of solid-SEDDS utilise a dynamic, two-phase *in vitro* lipolysis model that simulates both the gastric and intestinal phases of digestion [178]. This will eliminate the need to make poorly supported assumptions on the influence of gastric conditions on the solid-SEDDS structure and chemistry.

3.2.2. *Influence of Lipid-Solid Carrier Interactions on Drug Dissolution and Absorption*

Partitioning of solubilised poorly water-soluble drug molecules towards the aqueous phase requires the lipid component of solid-SEDDS to either (i) desorb from the solid carrier and partition towards the aqueous phase, or (ii) be hydrolysed to facilitate the release of lipid digestion products (for SEDDS containing digestible lipids); or alternatively, the solid carrier

to be solubilised within the GI tract. Thus, the affinity between the solid carrier and lipid species directly influences the solubilisation and absorption of encapsulated drug molecules within solid-SEDDS. This can be impacted by various solid carrier properties, including aqueous solubility, hydrophobicity, electrostatic interactions, propensity to aggregation and porosity [179], all of which are reviewed in the section below.

3.2.2.1. Impact of Solid Carrier Solubility

A study performed by Kang *et al.* [180] systematically analysed the impact of solid carrier physicochemical properties on the *in vivo* bioavailability of flurbiprofen, when formulated with self-emulsifying lipids. Solid-SEDDS were prepared by spray drying liquid-SEDDS with water-soluble (polyvinyl alcohol, PVA; Na-CMC) and water-insoluble carriers (fumed silica particles, Aerosil 200; and, magnesium stearate) at a ratio of 1:1. The extent of *in vitro* flurbiprofen dissolution after 60 minutes, when administered with water-soluble solid-SEDDS, was 1.6-2.5 times lower than that of water-insoluble solid-SEDDS and was comparable to the pure drug. However, analysis of the dissolution kinetics highlighted a sustained-release mechanism for both systems, whereby the rate of dissolution was linearly proportional to time. This indicated that PVA and Na-CMC retarded emulsification or release of the drug into the lipid phase, leading to a controlled release mechanism. Since this study did not compare the solid-SEDDS with the precursor liquid-SEDDS, it was difficult to estimate the influence of PVA and Na-CMC on SEDDS performance. However, physicochemical analysis of the solid-SEDDS revealed that PVA and Na-CMC solid-SEDDS were composed of a core-shell structure, whereby the solid component encapsulated the lipid phase. Since PVA and Na-CMC do not exert rapid dissolution kinetics in aqueous media [181, 182], it is stipulated that the rate of flurbiprofen dissolution was controlled by the rate

of solid carrier erosion/dissolution, which triggered the release and emulsification of the drug loaded lipid phase. *In vivo* assessments demonstrated that the sustained release mechanism of PVA and Na-CMC solid-SEDDS facilitated 4.4- and 11.1-fold enhancements in the AUC, respectively, compared to the pure drug [180].

Additional studies combining alternative water-soluble polymers, such as HPMC and synthetic poloxamers with liquid-SEDDS, have confirmed this controlled release mechanism for water-soluble solid-SEDDS [32, 115, 183]. Unlike water-insoluble polymers that exert dispersion- and diffusion-dependent release mechanisms, drug release from water-soluble polymeric carriers has been confirmed to be erosion-dependent [180]. Thus, it is possible to manipulate drug dissolution kinetics based on the propensity for the solid matrix to erode, swell or dissolve in the aqueous media. This was demonstrated by Yi *et al.* [184], who compared the *in vitro* dissolution rates of nimodipine in solid-SEDDS stabilised with HPMC of various viscosities. As expected, an increase in polymer viscosity correlated with a decrease in the rate of nimodipine release, due to the inhibition of drug diffusion through the denser HPMC matrix and a reduced rate in polymer erosion and dissolution [184].

The unique ability for water-soluble solid excipients to control drug dissolution based on changes in degradation and solubilisation rates poses opportunities for the use of alternate, novel excipients with promising drug delivery characteristics. Porous carbonate salts, specifically calcium carbonate and magnesium carbonate, have been successfully and safely applied as drug delivery vehicles for poorly water-soluble compounds [185-188], but have yet to be solely formulated with self-emulsifying lipids (at the time of review). Porous carbonate salts rapidly dissolve within aqueous media, especially under acidic conditions within the gastric environment [189, 190], which can facilitate fast and complete

emulsification of encapsulated lipids. Subsequently, this proposed solid-SEDDS is hypothesised to overcome incomplete lipid/drug release from solid carriers, making the entire payload available for absorption. Furthermore, carbonate salts are commonly employed as antacids due to their propensity to neutralise stomach acid [127], which can be exploited to overcome pH-sensitivity or precipitation concerns for key therapeutic compounds. However, design considerations are required for carbonates, since dose dumping and precipitation prior to reaching the absorptive site of the small intestine may restrict the biopharmaceutical performance of such solid-SEDDS, especially for compounds with limited solubilities in acidic media [127].

3.2.2.2. Impact of Solid Carrier Surface Chemistry

Surface chemistry regulates the affinity between lipid components and the solid carrier within solid-SEDDS, which subsequently alters the partitioning and emulsification kinetics of the lipid phase. This was clearly highlighted by Weerapool *et al.* [191] who compared the influence of particle wettability on the *in vitro* dissolution of nifedipine from solid-SEDDS, by employing hydrophilic (Aerosil 200) and hydrophobic porous silica particles (Aerosil R972) with similar nanostructures as the solid carrier. Particle hydrophobicity controlled the physicochemical properties of the fabricated hybrid particles, whereby hydrophilic porous silica formed free-flowing powders in contrast to the viscous oleogels formed upon sorption of lipids to the hydrophobic porous silica particles. The affinity between the lipid excipients and solid carrier was substantially greater for hydrophobic silica particles, which was evidenced by only 33% nifedipine dissolution in simulated gastric fluid being observed, compared to 80% for hydrophilic silica particles. Thus, the strong hydrophobic interactions between lipid and the hydrophobic surface retarded lipid diffusion and partitioning towards

the bulk dissolution media [163, 191]. While exploiting this mechanism may serve as a suitable approach to sustain the *in vivo* solubilisation of lipophilic drugs and thereby increase their residence time within the GI tract, formulating lipids and lipophilic drugs with hydrophobic porous particles has proven to be a challenging task due to associated incomplete drug release issues [146, 192, 193].

Investigations using aluminosilicates as adsorbents for the solidification of SEDDS have further highlighted the influence of surface chemistry on the affinity between lipids and the solid carrier. Smectite clay materials possess unique and complex surface chemistries, whereby octahedral metal oxide sheets are sandwiched between two tetrahedral silica sheets [194]. Owing to isomorphic substitution of some lattice cations for cations of lower valency, these materials carry a permanent negative platelet face charge, as well as a pH-dependent platelet edge charge due to lattice discontinuities and formation of exposed edge hydroxyl groups [195]. Due to this unique structure, smectite materials are capable of pH-dependent anion- and cation-exchange, which renders their use as adsorbents for lipids and charged drug molecules challenging.

Neusilin[®] US2, a specialised, pharmaceutical-grade amorphous magnesium aluminosilicate composed of mesoporous spherical granules (average particle size 44-177 μm , specific surface area 300 m^2/g , average pore size 5-6 nm) [127], has been one of the most extensively explored solid carriers for SEDDS due to its high adsorptive capacity and excellent tableting properties [12, 124, 196, 197]. However, Van Speybroeck *et al.* [125] highlighted the challenges associated with adsorbing SEDDS within Neusilin[®] US2. *In vitro* drug solubilisation under digesting and non-digesting fasted-state intestinal conditions was ~35% lower for Neusilin[®] US2 solid-SEDDS compared to the original liquid-SEDDS for both long-

and medium-chain SEDDS; leading to ~50% reduction in *in vivo* oral bioavailability of danazol. Further probing of the mechanisms involved in Neusilin[®] US2 solid-SEDDS indicated that drug molecules did not interact with the solid surface, but rather incomplete desorption of lipids from Neusilin was observed, leading to reduced SEDDS emulsification within the aqueous phase [126]. Specifically, larger emulsion droplets were formed for solid-SEDDS, which was attributed to the lower relative concentration of the surfactant Cremophor EL[®] within the aqueous phase. Thus, adsorptive interactions between SEDDS excipients and Neusilin[®] US2 was shown to be discriminatory, based on the affinity between key SEDDS species and the aluminosilicate surface [125, 126].

Studies performed by Dening *et al.* [119, 167, 198] further confirmed the high affinity between various lipid species and smectite clay materials. Novel solid-SEDDS were developed by spray drying dispersed submicron lipid droplets stabilised by montmorillonite and laponite. While it was expected that solidification with such solid carriers would result in equivalent or improved biopharmaceutical performance, *in vivo* pharmacokinetics of several lipophilic drugs demonstrated a reduction in oral absorption [119]. Further examination of the release mechanisms in clay-lipid hybrid materials confirmed lipid and drug desorption was incomplete, due to the ability for clay materials to adsorb and retain various lipid species. After 60 min *in vitro* intestinal lipolysis, it was found that between 55-90% of all lipid species remained adsorbed within montmorillonite and laponite matrices. Free fatty acids were found to have the greatest affinity for the clay particles, which was hypothesised to be due to attractive electrostatic interactions between the positively-charged platelet edges and negatively-charged fatty acids [198]. Additional studies demonstrated that nanostructured clay particles (when dosed without lipid) adsorb 25-80% of emulsified lipid species from the aqueous phase of simulated intestinal fluid, under both digesting and non-digestion

conditions. *In vitro* drug dissolution correlated with these observations for clay-lipid hybrid particles, whereby aqueous partitioning of poorly water-soluble drug molecules was proportional to lipid partitioning [167]. Thus, while smectite clays are commonly considered as excellent candidates for the solidification of liquid-SEDDS due to their high adsorptive capacities, mesoporosity and good tabletability, selective design considerations are required to overcome limitations associated with lipid and drug retention [127].

3.2.2.3. Impact of Solid Carrier Porous Nanostructure

Chavan *et al.* [199] recently investigated the influence of porous nanostructure of solid-SEDDS on the oral bioavailability of celecoxib. This was achieved by physically adsorbing SEDDS (composed of a 10:45:45% v/v mixture of Capryol 90: Tween 20: Transcutol HP, with Soluplus as a precipitation inhibitor) onto hydrophilic porous silica particles with varying surface areas, particle sizes and pore structures. Specifically, micronised silica (Sylysia 350; surface area: 300 m²/g, average particle size: 3.9 µm) was compared to two different types of fumed silica (Aerosil 300; surface area 300 m²/g, average particle size: 50-500 nm; and, Aerosil 200; surface area 200 m²/g, average particle size: 50-500 nm). Physicochemical investigations of the three solid-SEDDS revealed that Sylysia 350 maintained a greater surface area post-lipid adsorption, due to the formation of smaller agglomerates, compared to the Aerosil solid-SEDDS. *In vitro* dissolution kinetics of celecoxib directly correlated with the surface area (and agglomerate size) of solid-SEDDS, whereby an increase in surface area (and decrease in agglomerate size) increased the rate and extent of drug dissolution. That is, an increase in surface area and reduction in agglomerate particle size increases the contact area and accessibility for dissolution media to diffuse into the porous structures, and thus, trigger the release of lipid excipients and drug molecules.

Furthermore, the mesoporous structure of Sylysia 350 was hypothesised to allow continuous ingress of dissolution media into the core of the hybrid particles, which was likely prohibited by the small, restrictive pores (< 7 nm) that can form within Aerosil agglomerates [146, 199]. Subsequently, the dissolution efficiencies for each solid-SEDDS were Sylysia 350 (13.5%) $>$ Aerosil 300 (2.4%) $>$ Aerosil 200 (0.9%). These findings were supported by Agarwal *et al.* [124] who demonstrated that griseofulvin dissolution correlated with an increase in carrier particle surface area for various silica and silicate solid-SEDDS. Dissolution was found to be dependent on the pore length and drug nucleation at the lipid/adsorbent interface [124].

So far, studies focused on investigating the role of porous nanostructure on solid-SEDDS pharmacokinetic performance have utilised porous carriers with poorly defined pore sizes and structures. Porous excipients with random pore sizes and structures, such as Aerosil fumed silica, are the most commonly employed carriers for solid-SEDDS due to their approval for use as pharmaceutical excipients. While this is a key consideration when selecting a solid excipient, the mechanistic insights that can be derived regarding the lipid: solid carrier interaction are limited. To this extent, opportunities exist to further probe the mechanisms that control *in vitro* drug dissolution from nanostructured solid-SEDDS by incorporating SEDDS within solid carriers with well-defined porous architectures, such as mesoporous silica nanoparticles. Quan *et al.* [122] successfully demonstrated the ability to enhance oral bioavailability of fenofibrate when combining SBA-15 mesoporous silica particles, composed of hexagonal structured and uniformly-sized pore networks, with SEDDS. By extending this work to include particles with various pore sizes and structures it will be possible to determine the role of microporosity, surface morphology and pore curvature on the mechanism of lipid and drug diffusion.

3.3 Therapeutic Compound

3.3.1. Drug-Solid Carrier Interactions

Whilst research into solid-SEDDS has progressed over the last decade, many studies neglect to compare the *in vitro* and/or *in vivo* performance of solid-SEDDS with the original liquid-SEDDS to gauge the impact of solidification. Of the studies that do compare liquid- and solid-SEDDS, data is often conflicting, with some studies demonstrating an equivalent performance and others showing significant differences in biopharmaceutical performance. In several cases, an inferior performance of solid-SEDDS relative to liquid-SEDDS has been observed [125, 126, 200] and this can be attributed to a variety of factors, including SEDDS-carrier interactions (see Section 3.2.2) as well as drug-carrier interactions.

Studies by Williams and colleagues [126] explored the potential mechanisms behind the inferior performance of solid-SEDDS prepared using Neusilin US2 via physical mixing in comparison to liquid-SEDDS. Incomplete drug release/desorption was observed for all four model drugs (danazol, fenofibrate, cinnarizine and mefenamic acid) encapsulated within solid-SEDDS. Interestingly, drug ionisation tendency was observed to significantly influence desorption. For the weak base cinnarizine, desorption from solid-SEDDS was greater in simulated gastric fluid (SGF; pH 1.2) than in simulated intestinal fluid (SIF; pH 6.5). In SGF, surface silanols of Neusilin (pKa 3.5) and basic cinnarizine molecules (pKa 7.5) are both protonated, and electrostatic repulsion enhances drug desorption from solid-SEDDS under these conditions. In contrast, however, Neusilin silanols are ionised in SIF at pH 6.5 and may electrostatically interact with positively charged cinnarizine molecules, thus retarding drug release. Further investigations regarding the influence of aluminosilicate surface chemistry on drug dissolution were performed by Krupa *et al.* [201], whereby ibuprofen loaded solid-

SEDDS were fabricated with Neusilin[®] US2 and amino-functionalised Neusilin[®] SG2. When formulated with equivalent SEDDS concentrations, the extent of *in vitro* drug dissolution was ~1.4-fold greater for Neusilin[®] US2 solid-SEDDS, compared to Neusilin[®] SG2 solid-SEDDS. The reduced dissolution induced by amino-functionalised Neusilin[®] SG2 was attributed to attractive electrostatic interactions between ionised ibuprofen carboxylic acid groups and amine groups on the aluminosilicate surface, leading to a higher affinity between drug molecules and the solid carrier [201]. These studies therefore highlight the potential issue of electrostatic or ion-exchange interactions between inorganic silica-based carrier materials and basic drugs.

Studies by Denning *et al.* [119] observed similar results when comparing a control lipid solution formulation with its corresponding solid-SEDDS using Aerosil 300 silica nanoparticles and montmorillonite clay for the poorly soluble weak base, blonanserine. Whilst the silicon dioxide-based solid-SEDDS was able to preserve the *in vitro* and *in vivo* performance of the simple lipid solution, the montmorillonite-based solid-SEDDS significantly decreased *in vitro* drug solubilisation 3-fold and *in vivo* bioavailability 6-fold, due to cation-exchange interactions between blonanserine and montmorillonite. Since the silica system performed well, it would appear that the issue of ion-exchange interactions with basic drug molecules may be unique to silicate-based materials such as Neusilin and montmorillonite, and caution should therefore be exercised when using silicates to solidify SEDDS of weak base drugs.

4. Future Perspectives for the Successful Development of Solid-SEDDS

The development of solid-SEDDS has significantly advanced the therapeutic and commercial potential of SEDDS. Solid-SEDDS are considered state-of-the-art delivery vehicles for poorly water-soluble drugs and afford considerable advantages over alternative liquid-LBDDS due to improved stability and drug loading, precise dosing, ease of handling and storage and improved patient compliance [202]. While increasing attention has been attributed to developing solid-SEDDS, little work has focused on the key formulation characteristics that influence *in vivo* drug absorption. Furthermore, few studies have focused on comparing solid-SEDDS delivery performance to the precursor liquid-SEDDS. Subsequently, in depth systematic analyses of the mechanistic interactions between drug molecules, solid carriers and lipid excipients are required to optimise *in vivo* absorption of drug molecules confined within solid-SEDDS and uncover their full therapeutic potential.

Firstly, this can be achieved by comparing and contrasting the solubilisation behaviour and *in vivo* pharmacokinetics of various drugs encapsulated within liquid- and solid-SEDDS. Secondly, to investigate and probe the interactions within solid-SEDDS on the nanoscale, it is suggested that a range of powerful physicochemical, surface sensitive and biophysical analysis techniques are used to elucidate the optimal parameters that facilitate improved biopharmaceutical performance for given therapeutics. Proposed analysis techniques useful for deriving structure-activity relationships for solid-SEDDS include, but are not limited to:

- (i) Waveguide evanescent-field microscopy: utilising label-free surface sensitive microscopy techniques, such as waveguide microscopy, introduces the ability for sub-molecular interactions to be probed at high resolution [203]. Thus, the key biophysical interactions that control drug solubilisation and dissolution can be

monitored at a single emulsion droplet level, which will facilitate improved predictability of solid-SEDDS performance in the bulk phase.

- (ii) Nano-Infrared (nano-IR): nano-IR allows for direct measurements of sample absorption, with submonolayer precision of <10 nm [204], by combining resonance enhanced atomic force microscopy with infrared spectroscopy. In doing so, spectra obtained correlates closely to that of bulk IR spectra and can provide key insights into the drug:lipid:solid carrier interaction prior to, during and after *in vitro* assessments, such as dissolution and lipolysis [198].
- (iii) Time-of-flight secondary ion mass spectrometry (ToF-SIMS): analysis of molecular fragmentation using ToF-SIMS allows for highly sensitive detection and *in situ* mapping of molecular associations within solid-state pharmaceuticals [205]. By sputter/depth profiling solid-SEDDS matrices, it is possible to obtain a three-dimensional cross-section that provides qualitative information regarding the spatial distribution of drug and lipid within the solid carrier [206]. Furthermore, ToF-SIMS has been used extensively to probe protein interactions, conformation and orientation within solid-state systems [207-209], which can be further harnessed to probe the lipid digestion mechanism within solid-SEDDS [162, 163]. Insights into the spatial arrangement and lipase interactions within solid-SEDDS will facilitate improved understanding of the dissolution mechanisms, affinity between drug, lipid and solid carrier, and will enable further optimisation of such formulations, by developing methods to evenly distribute drug molecules within the solid and lipid phases.

By combining these characterisation techniques with conventional *in vitro* and *in vivo* pharmaceutical assessments, it will be possible to derive structure-activity relationships that aid as a predictive tool for designing solid-SEDDS with optimal delivery performance for the therapeutic of interest. Furthermore, the improved understanding of drug: lipid: solid carrier interactions gained from these investigations will lead to improved pharmacokinetic performance and stronger *in vitro-in vivo* correlations when lipophilic drugs are encapsulated within solid-SEDDS.

5. Conclusions

Solid-SEDDS have emerged as a promising approach to harness and couple the solubilisation capacity of SEDDS with the stabilising effect of solid excipients for overcoming key limitations associated with liquid-SEDDS. The formation of solid-SEDDS has introduced the ability to finely manipulate the physicochemical properties and delivery mechanisms, so that the solubilisation capacity and pharmacokinetic performance of poorly water-soluble drugs can be optimised. However, several studies have demonstrated that solid-SEDDS provide an inferior *in vivo* pharmacokinetic profile relative to the original liquid-SEDDS. Despite this, the performance of solid-SEDDS is typically significantly improved relative to crystalline drug material. Thus, the benefits attributed to formulating SEDDS as a solid dosage form need to be weighed against any potential decrease in biopharmaceutical performance that solidification brings on an individual basis. By continuing to explore and develop innovative synthesis techniques and formulation excipients, as well as advancing current characterisation and assessment methodologies, more insightful understanding of the mechanisms that control dissolution of lipophilic drugs will be granted, which will allow for

the full therapeutic potential of a wide range of challenging bioactive compounds to be discovered.

Table 1: Considerations when selecting a technique to solidify SEDDS.

Technique	Key concept/process	Primary approach		Form of precursor liquid SEDDS		Physical form of resulting product	Possible thermal stability issues?	Max reported Drug Load (% w/w) [9]	Max reported Lipid Load (% w/w) [9] *not from [9]	Best suited for what drug dose/potency?	Rate of self-emulsification upon oral administration	Control over solidification conditions	References
		To simply solidify	To induce change in performance	Excipients	Pre-emulsified								
Physical adsorption to solid carriers	Adsorption of SEDDS to the solid carrier via mixing with a blender.	X	X	X	X	Powder or granules		10	80	Low dose, high potency	++	+	[50, 198-200]
Hot/melt granulation/extrusion	High shear mixing of SEDDS and a solid carrier. Followed by optional forcing through a die.	X		X		Granules (agglomerates) which can be extruded into pellets of different shapes and sizes	X (during high shear mixing and if using molten SEDDS)	80	50	Low-medium dose	++	++	[201-205]
Freeze drying	Sublimation of the aqueous phase from frozen SEDDS stabilised by a carrier material.	X	X	X	X	Powder or granules (porous agglomerates)	X (<0°C to freeze, consider using a cryoprotectant)	50*	60*	Low dose, high potency	+++	++	[124, 133, 206, 207]
Spray drying	Evaporation of solvent from atomized spray of SEDDS (stabilised by a solid material) at high temperature.	X	X	X	X	Powder or granules (porous and spherical particles)	X (short exposure to high temperature - max 220 °C)	50	60	Low dose, high potency	+++	+++	[37, 115, 146, 208-213]

Acknowledgements: The Australian Research Council's Centre of Excellence in Convergent Bio-Nano Science and Technology (ARC CE140100036), the ÅForsk Foundation (16-463) and UniSA Ventures are greatly acknowledged for research funding and support. The Australian Government Research Training Program is acknowledged for the PhD Scholarships of Tahnee J. Dening, Tahlia Meola and Hayley Schultz.

6. References

- [1] A. Tan, S. Rao, C.A. Prestidge, Transforming Lipid-Based Oral Drug Delivery Systems into Solid Dosage Forms: An Overview of Solid Carriers, Physicochemical Properties, and Biopharmaceutical Performance, *Pharm. Res.*, 30 (2013) 2993-3017.
- [2] C.J.H. Porter, N.L. Trevaskis, W.N. Charman, Lipids and lipid-based formulations: optimising the oral delivery of lipophilic drugs, *Nat. Rev. Drug Discov.*, 6 (2007) 231-248.
- [3] C.W. Pouton, C.J.H. Porter, Formulation of lipid-based delivery systems for oral administration: Materials, methods and strategies, *Adv. Drug Del. Rev.*, 60 (2008) 625-637.
- [4] A.J. Humberstone, W.N. Charman, Lipid-based vehicles for the oral delivery of poorly water soluble drugs, *Adv. Drug Del. Rev.*, 25 (1997) 103-128.
- [5] R.N. Gursoy, S. Benita, Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs, *Biomed. Pharmacother.*, 58 (2004) 173-182.
- [6] P.P. Constantinides, Lipid microemulsions for improving drug dissolution and oral absorption: Physical and biopharmaceutical aspects, *Pharm. Res.*, 12 (1995) 1561-1572.
- [7] A. Abdalla, S. Klein, K. Mäder, A new self-emulsifying drug delivery system (SEDDS) for poorly soluble drugs: characterization, dissolution, in vitro digestion and incorporation into solid pellets, *Eur. J. Pharm. Sci.*, 35 (2008) 457-464.
- [8] M.M. Nerurkar, P.S. Burton, R.T. Borchardt, The use of surfactants to enhance the permeability of peptides through Caco-2 cells by inhibition of an apically polarized efflux system, *Pharm. Res.*, 13 (1996) 528-534.
- [9] V. Jannin, J. Musakhanian, D. Marchaud, Approaches for the development of solid and semi-solid lipid-based formulations, *Adv. Drug Del. Rev.*, 60 (2008) 734-746.
- [10] J. Mandić, A. Zvonar Pobirk, F. Vrečer, M. Gašperlin, Overview of solidification techniques for self-emulsifying drug delivery systems from industrial perspective, *Int. J. Pharm.*, 533 (2017) 335-345.
- [11] D.G. Fatouros, D.M. Karpf, F.S. Nielsen, A. Mullertz, Clinical studies with oral lipid based formulations of poorly soluble compounds, *Ther. Clin. Risk Manag.*, 3 (2007) 591-604.
- [12] B. Tang, G. Cheng, J.-C. Gu, C.-H. Xu, Development of solid self-emulsifying drug delivery systems: Preparation techniques and dosage forms, *Drug Discov. Today*, 13 (2008) 606-612.
- [13] S. Kollipara, R.K. Gandhi, Pharmacokinetic aspects and in vitro–in vivo correlation potential for lipid-based formulations, *Acta Pharmaceutica Sinica B*, 4 (2014) 333-349.
- [14] A. Sharma, U.S. Sharma, Liposomes in drug delivery: progress and limitations, *Int. J. Pharm.*, 154 (1997) 123-140.
- [15] D. Fleisher, C. Li, Y. Zhou, L.-H. Pao, A. Karim, Drug, meal and formulation interactions influencing drug absorption after oral administration, *Clin. Pharmacokinet.*, 36 (1999) 233-254.
- [16] Y. Zhang, R. Wang, J. Wu, Q. Shen, Characterization and evaluation of self-microemulsifying sustained-release pellet formulation of puerarin for oral delivery, *Int. J. Pharm.*, 427 (2012) 337-344.
- [17] S. Setthacheewakul, W. Kedjinda, D. Maneenuan, R. Wiwattanapatapee, Controlled release of oral tetrahydrocurcumin from a novel self-emulsifying floating drug delivery system (SEFDDS), *AAPS PharmSciTech*, 12 (2011) 152-164.
- [18] S. Rao, K. Richter, T.-H. Nguyen, B. Boyd, C.J.H. Porter, A. Tan, C.A. Prestidge, Pluronic-Functionalized Silica Lipid Hybrid Microparticles: Improving the Oral Delivery of Poorly Water-Soluble Weak Bases, *Mol. Pharm.*, 12 (2015) 4424-4433.

- [19] P. Joyce, C.P. Whitby, C.A. Prestidge, Bioactive Hybrid Particles from Poly(d,l-lactide-co-glycolide) Nanoparticle Stabilized Lipid Droplets, *ACS Appl. Mater. Interfaces*, 7 (2015) 17460-17470.
- [20] P. Joyce, C.A. Prestidge, Synergistic effect of PLGA nanoparticles and submicron triglyceride droplets in enhancing the intestinal solubilisation of a lipophilic weak base, *Eur. J. Pharm. Sci.*, 118 (2018) 40-48.
- [21] J. Aungst Bruce, Intestinal permeation enhancers, *J. Pharm. Sci.*, 89 (2000) 429-442.
- [22] M. Thanou, J.C. Verhoef, H.E. Junginger, Chitosan and its derivatives as intestinal absorption enhancers, *Adv. Drug Del. Rev.*, 50 (2001) S91-S101.
- [23] S. Kanuganti, R. Jukanti, P.R. Veerareddy, S. Bandari, Paliperidone-loaded self-emulsifying drug delivery systems (SEDDS) for improved oral delivery, *J. Dispersion Sci. Technol.*, 33 (2012) 506-515.
- [24] N. Sermkaew, K. Wiwattanawongsa, W. Ketjinda, R. Wiwattanapatapee, Development, characterization and permeability assessment based on Caco-2 monolayers of self-microemulsifying floating tablets of tetrahydrocurcumin, *AAPS PharmSciTech*, 14 (2013) 321-331.
- [25] B. Chatterjee, S. Hamed Almurisi, A. Ahmed Mahdi Dukhan, U.K. Mandal, P. Sengupta, Controversies with self-emulsifying drug delivery system from pharmacokinetic point of view, *Drug Deliv.*, 23 (2016) 3639-3652.
- [26] H.D. Williams, M.U. Anby, P. Sassene, K. Kleberg, J.-C. Bakala-N'Goma, M. Calderone, V. Jannin, A. Igonin, A. Partheil, D. Marchaud, E. Jule, J. Vertommen, M. Maio, R. Blundell, H. Benameur, F. Carrière, A. Müllertz, C.W. Pouton, C.J.H. Porter, Toward the Establishment of Standardized in Vitro Tests for Lipid-Based Formulations. 2. The Effect of Bile Salt Concentration and Drug Loading on the Performance of Type I, II, IIIA, IIIB, and IV Formulations during in Vitro Digestion, *Mol. Pharm.*, 9 (2012) 3286-3300.
- [27] H. Zhou, J. Wan, L. Wu, T. Yi, W. Liu, H. Xu, X. Yang, A New Strategy for Enhancing the Oral Bioavailability of Drugs with Poor Water-Solubility and Low Liposolubility Based on Phospholipid Complex and Supersaturated SEDDS, *PLoS One*, 8 (2014) e84530.
- [28] H.B. Schultz, N. Thomas, S. Rao, C.A. Prestidge, Supersaturated silica-lipid hybrids (super-SLH): An improved solid-state lipid-based oral drug delivery system with enhanced drug loading, *Eur. J. Pharm. Biopharm.*, 125 (2018) 13-20.
- [29] A. Tan, C. Prestidge, Nanostructured silica-lipid hybrid microparticles: a supersaturating carrier for water-and lipid-resistant compounds, *Chem. Lett.*, 41 (2012) 1334-1336.
- [30] G. Quan, B. Niu, V. Singh, Y. Zhou, C.-Y. Wu, X. Pan, C. Wu, Supersaturable solid self-microemulsifying drug delivery system: precipitation inhibition and bioavailability enhancement, *International journal of nanomedicine*, 12 (2017) 8801-8811.
- [31] W.H. Song, J.H. Park, D.W. Yeom, B.K. Ahn, K.M. Lee, S.G. Lee, H.S. Woo, Y.W. Choi, Enhanced dissolution of celecoxib by supersaturating self-emulsifying drug delivery system (S-SEDDS) formulation, *Arch. Pharm. Res.*, 36 (2013) 69-78.
- [32] Y. Chen, C. Chen, J. Zheng, Z. Chen, Q. Shi, H. Liu, Development of a Solid Supersaturable Self-Emulsifying Drug Delivery System of Docetaxel with Improved Dissolution and Bioavailability, *Biol. Pharm. Bull.*, 34 (2011) 278-286.
- [33] Y. He, S. Liang, M. Long, H. Xu, Mesoporous silica nanoparticles as potential carriers for enhanced drug solubility of paclitaxel, *Materials Science and Engineering: C*, 78 (2017) 12-17.

- [34] S. Rao, A. Tan, B.J. Boyd, C.A. Prestidge, Synergistic role of self-emulsifying lipids and nanostructured porous silica particles in optimizing the oral delivery of lovastatin, *Nanomedicine*, 9 (2014) 2745-2759.
- [35] A. Tan, S. Simovic, A.K. Davey, T. Rades, C.A. Prestidge, Silica-lipid hybrid (SLH) microcapsules: A novel oral delivery system for poorly soluble drugs, *J. Control. Release*, 134 (2009) 62-70.
- [36] T.J. Dening, S. Rao, N. Thomas, C.A. Prestidge, Silica encapsulated lipid-based drug delivery systems for reducing the fed/fasted variations of ziprasidone in vitro, *Eur. J. Pharm. Biopharm.*, 101 (2016) 33-42.
- [37] R. Yasmin, S. Rao, K. Bremmell, C. Prestidge, Synergistic role of solid lipid and porous silica in improving the oral delivery of weakly basic poorly water soluble drugs, *Eur. J. Pharm. Sci.*, 96 (2017) 508-514.
- [38] E. Shoghi, E. Fuguet, E. Bosch, C. Ràfols, Solubility-pH profiles of some acidic, basic and amphoteric drugs, *Eur. J. Pharm. Sci.*, 48 (2013) 291-300.
- [39] S. Li, P. Doyle, S. Metz, A.E. Royce, A.T.M. Serajuddin, Effect of Chloride ion on Dissolution of Different Salt Forms of Haloperidol, a Model Basic Drug, *J. Pharm. Sci.*, 94 (2005) 2224-2231.
- [40] N. Thomas, R. Holm, M. Garmer, J.J. Karlsson, A. Müllertz, T. Rades, Supersaturated Self-Nanoemulsifying Drug Delivery Systems (Super-SNEDDS) Enhance the Bioavailability of the Poorly Water-Soluble Drug Simvastatin in Dogs, *The AAPS Journal*, 15 (2013) 219-227.
- [41] D.B. Warren, C.A.S. Bergström, H. Benameur, C.J.H. Porter, C.W. Pouton, Evaluation of the Structural Determinants of Polymeric Precipitation Inhibitors Using Solvent Shift Methods and Principle Component Analysis, *Mol. Pharm.*, 10 (2013) 2823-2848.
- [42] P. Balani, S. Wong, W. Ng, E. Widjaja, R. Tan, S. Chan, Influence of polymer content on stabilizing milled amorphous salbutamol sulphate, *Int. J. Pharm.*, 391 (2010) 125-136.
- [43] K.W.Y. Lee, C.J.H. Porter, B.J. Boyd, The Effect of Administered Dose of Lipid-Based Formulations on the In Vitro and In Vivo Performance of Cinnarizine as a Model Poorly Water-Soluble Drug, *J. Pharm. Sci.*, 102 (2013) 565-578.
- [44] P. Joyce, R. Yasmin, A. Bhatt, B.J. Boyd, A. Pham, C.A. Prestidge, Comparison across Three Hybrid Lipid-Based Drug Delivery Systems for Improving the Oral Absorption of the Poorly Water-Soluble Weak Base Cinnarizine, *Mol. Pharm.*, 14 (2017) 4008-4018.
- [45] M. Van Speybroeck, R. Mols, R. Mellaerts, T. Do Thi, J.A. Martens, J. Van Humbeeck, P. Annaert, G. Van den Mooter, P. Augustijns, Combined use of ordered mesoporous silica and precipitation inhibitors for improved oral absorption of the poorly soluble weak base itraconazole, *Eur. J. Pharm. Biopharm.*, 75 (2010) 354-365.
- [46] C. Brough, D.A. Miller, D. Ellenberger, D. Lubda, R.O. Williams, Use of Polyvinyl Alcohol as a Solubility Enhancing Polymer for Poorly Water-Soluble Drug Delivery (Part 2), *AAPS PharmSciTech*, 17 (2016) 180-190.
- [47] C. Brough, D.A. Miller, J.M. Keen, S.A. Kucera, D. Lubda, R.O. Williams, Use of Polyvinyl Alcohol as a Solubility-Enhancing Polymer for Poorly Water Soluble Drug Delivery (Part 1), *AAPS PharmSciTech*, 17 (2016) 167-179.
- [48] J.-Y. Hong, J.-K. Kim, Y.-K. Song, J.-S. Park, C.-K. Kim, A new self-emulsifying formulation of itraconazole with improved dissolution and oral absorption, *J. Control. Release*, 110 (2006) 332-338.
- [49] R. Mellaerts, J.A.G. Jammaer, M. Van Speybroeck, H. Chen, J.V. Humbeeck, P. Augustijns, G. Van den Mooter, J.A. Martens, Physical State of Poorly Water Soluble

Therapeutic Molecules Loaded into SBA-15 Ordered Mesoporous Silica Carriers: A Case Study with Itraconazole and Ibuprofen, *Langmuir*, 24 (2008) 8651-8659.

[50] R. Mellaerts, R. Mols, P. Kayaert, P. Annaert, J. Van Humbeeck, G. Van den Mooter, J.A. Martens, P. Augustijns, Ordered mesoporous silica induces pH-independent supersaturation of the basic low solubility compound itraconazole resulting in enhanced transepithelial transport, *Int. J. Pharm.*, 357 (2008) 169-179.

[51] H. Kranz, T. Wagner, Effects of formulation and process variables on the release of a weakly basic drug from single unit extended release formulations, *Eur. J. Pharm. Biopharm.*, 62 (2006) 70-76.

[52] C. Guse, S. Koennings, F. Kreye, F. Siepmann, A. Göpfertich, J. Siepmann, Drug release from lipid-based implants: elucidation of the underlying mass transport mechanisms, *Int. J. Pharm.*, 314 (2006) 137-144.

[53] Z.P. Aguilar, Chapter 5 - Targeted Drug Delivery, *Nanomaterials for Medical Applications*, Elsevier2013, pp. 181-234.

[54] H.K. Makadia, S.J. Siegel, Poly Lactic-co-Glycolic Acid (PLGA) as Biodegradable Controlled Drug Delivery Carrier, *Polymers*, 3 (2011) 1377-1397.

[55] W.J. Gun, A.F. Routh, Formation and Characterization of pH-Responsive Liquid Core Microcapsules, *Langmuir*, 29 (2013) 12541-12548.

[56] R. Negrini, R. Mezzenga, pH-Responsive Lyotropic Liquid Crystals for Controlled Drug Delivery, *Langmuir*, 27 (2011) 5296-5303.

[57] G. Dollo, P. Le Corre, A. Guérin, F. Chevanne, J.L. Burgot, R. Leverge, Spray-dried redispersible oil-in-water emulsion to improve oral bioavailability of poorly soluble drugs, *Eur. J. Pharm. Sci.*, 19 (2003) 273-280.

[58] I.Y. Galaev, B. Mattiasson, 'Smart' polymers and what they could do in biotechnology and medicine, *Trends Biotechnol.*, 17 (1999) 335-340.

[59] D. Dupin, S. Fujii, S.P. Armes, P. Reeve, S.M. Baxter, Efficient synthesis of sterically stabilized pH-responsive microgels of controllable particle diameter by emulsion polymerization, *Langmuir*, 22 (2006) 3381-3387.

[60] Q. Yang, S. Wang, P. Fan, L. Wang, Y. Di, K. Lin, F.-S. Xiao, pH-responsive carrier system based on carboxylic acid modified mesoporous silica and polyelectrolyte for drug delivery, *Chem. Mater.*, 17 (2005) 5999-6003.

[61] E. Toorisaka, M. Hashida, N. Kamiya, H. Ono, Y. Kokazu, M. Goto, An enteric-coated dry emulsion formulation for oral insulin delivery, *J. Control. Release*, 107 (2005) 91-96.

[62] E. Toorisaka, H. Ono, K. Arimori, N. Kamiya, M. Goto, Hypoglycemic effect of surfactant-coated insulin solubilized in a novel solid-in-oil-in-water (S/O/W) emulsion, *Int. J. Pharm.*, 252 (2003) 271-274.

[63] S. Gupta, R. Kesarla, A. Omri, Formulation Strategies to Improve the Bioavailability of Poorly Absorbed Drugs with Special Emphasis on Self-Emulsifying Systems, *ISRN Pharmaceutics*, 2013 (2013) 848043.

[64] A.K. Gurram, P.B. Deshpande, S.S. Kar, U.Y. Nayak, N. Udupa, M.S. Reddy, Role of Components in the Formation of Self-microemulsifying Drug Delivery Systems, *Indian J. Pharm. Sci.*, 77 (2015) 249-257.

[65] T. Yu, K. Greish, L.D. McGill, A. Ray, H. Ghandehari, Influence of geometry, porosity, and surface characteristics of silica nanoparticles on acute toxicity: their vasculature effect and tolerance threshold, *ACS NANO*, 6 (2012) 2289.

- [66] P. Gao, B.D. Rush, W.P. Pfund, T. Huang, J.M. Bauer, W. Morozowich, M.-S. Kuo, M.J. Hageman, Development of a supersaturable SEDDS (S-SEDDS) formulation of paclitaxel with improved oral bioavailability, *J. Pharm. Sci.*, 92 (2003) 2386-2398.
- [67] P. Gao, M.E. Guyton, T. Huang, J.M. Bauer, K.J. Stefanski, Q. Lu, Enhanced Oral Bioavailability of a Poorly Water Soluble Drug PNU- 91325 by Supersaturatable Formulations, *Drug Dev. Ind. Pharm.*, 30 (2004) 221-229.
- [68] U.S.F.a.D. Administration, Generally Reconized as Safe (GRAS), 2018.
- [69] S. Ghnimi, E. Budilarto, A. Kamal- Eldin, The New Paradigm for Lipid Oxidation and Insights to Microencapsulation of Omega- 3 Fatty Acids, *Compr. Rev. Food Sci. Food Saf.*, 16 (2017) 1206-1218.
- [70] M. D.J., D. E.A., Lipid Oxidation in Oil- in- Water Emulsions: Impact of Molecular Environment on Chemical Reactions in Heterogeneous Food Systems, *J. Food Sci.*, 65 (2000) 1270-1282.
- [71] S.J. Lee, S.J. Choi, Y. Li, E.A. Decker, D.J. McClements, Protein-stabilized nanoemulsions and emulsions: comparison of physicochemical stability, lipid oxidation, and lipase digestibility, *J. Agric. Food. Chem.*, 59 (2010) 415-427.
- [72] C. Tengroth, U. Gasslander, F.O. Andersson, S.P. Jacobsson, Cross-Linking of Gelatin Capsules with Formaldehyde and Other Aldehydes: An FTIR Spectroscopy Study, *Pharm. Dev. Technol.*, 10 (2005) 405-412.
- [73] G.A. Digenis, T.B. Gold, V.P. Shah, Cross- Linking of Gelatin Capsules and Its Relevance to Their in Vitro-in Vivo Performance, *J. Pharm. Sci.*, 83 (1994) 915-921.
- [74] R. Khanum, H. Thevanayagam, Lipid peroxidation: Its effects on the formulation and use of pharmaceutical emulsions, *Asian Journal of Pharmaceutical Sciences*, 12 (2017) 401-411.
- [75] X.D. Chen, A.S. Mujumdar, *Drying technologies in food processing*, John Wiley & Sons 2009.
- [76] P.J. Fellows, *Food processing technology: principles and practice*, Elsevier 2009.
- [77] M. Kargar, F. Spyropoulos, I.T. Norton, Microstructural design to reduce lipid oxidation in oil-in-water emulsions, *Procedia Food Science*, 1 (2011) 104-108.
- [78] C.C. Berton- Carabin, M.H. Ropers, C. Genot, Lipid Oxidation in Oil- in- Water Emulsions: Involvement of the Interfacial Layer, *Compr. Rev. Food Sci. Food Saf.*, 13 (2014) 945-977.
- [79] E.S. Budilarto, A. Kamal-Eldin, The supramolecular chemistry of lipid oxidation and antioxidation in bulk oils, *Eur. J. Lipid Sci. Technol.*, 117 (2015) 1095-1137.
- [80] P. Siani, R.M. de Souza, L.G. Dias, R. Itri, H. Khandelia, An overview of molecular dynamics simulations of oxidized lipid systems, with a comparison of ELBA and MARTINI force fields for coarse grained lipid simulations, *Biochim. Biophys. Acta*, 1858 (2016) 2498-2511.
- [81] V.D. Kancheva, O.T. Kasaikina, Lipid Oxidation in Homogeneous and Micro-heterogeneous Media in Presence of Prooxidants, Antioxidants and Surfactants, *Lipid Peroxidation*, InTech 2012.
- [82] N. Garti, *Delivery and controlled release of bioactives in foods and nutraceuticals*, Elsevier 2008.
- [83] H. Yuji, J. Weiss, P. Villeneuve, L.J. López Giraldo, M.-C. Figueroa-Espinoza, E.A. Decker, Ability of Surface-Active Antioxidants To Inhibit Lipid Oxidation in Oil-in-Water Emulsion, *J. Agric. Food. Chem.*, 55 (2007) 11052-11056.

- [84] W. Chaiyasit, R.J. Elias, D.J. McClements, E.A. Decker, Role of physical structures in bulk oils on lipid oxidation, *Crit. Rev. Food Sci. Nutr.*, 47 (2007) 299-317.
- [85] M. Kargar, K. Fayazmanesh, M. Alavi, F. Spyropoulos, I.T. Norton, Investigation into the potential ability of Pickering emulsions (food-grade particles) to enhance the oxidative stability of oil-in-water emulsions, *J. Colloid Interface Sci.*, 366 (2012) 209-215.
- [86] M. Kargar, F. Spyropoulos, I.T. Norton, The effect of interfacial microstructure on the lipid oxidation stability of oil-in-water emulsions, *J. Colloid Interface Sci.*, 357 (2011) 527-533.
- [87] F. Liu, C.-H. Tang, Soy Protein Nanoparticle Aggregates as Pickering Stabilizers for Oil-in-Water Emulsions, *J. Agric. Food. Chem.*, 61 (2013) 8888-8898.
- [88] Z. Cui, X. Kong, Y. Chen, C. Zhang, Y. Hua, Effects of rutin incorporation on the physical and oxidative stability of soy protein-stabilized emulsions, *Food Hydrocoll.*, 41 (2014) 1-9.
- [89] M.S. Katsuda, D. McClements, L.H. Miglioranza, E.A. Decker, Physical and oxidative stability of fish oil-in-water emulsions stabilized with β -lactoglobulin and pectin, *J. Agric. Food. Chem.*, 56 (2008) 5926-5931.
- [90] C. Sun, S. Gunasekaran, M.P. Richards, Effect of xanthan gum on physicochemical properties of whey protein isolate stabilized oil-in-water emulsions, *Food Hydrocoll.*, 21 (2007) 555-564.
- [91] S. Drusch, Y. Serfert, M. Scampicchio, B. Schmidt-Hansberg, K. Schwarz, Impact of Physicochemical Characteristics on the Oxidative Stability of Fish Oil Microencapsulated by Spray-Drying, *J. Agric. Food. Chem.*, 55 (2007) 11044-11051.
- [92] Y. Minemoto, K. Hakamata, S. Adachi, R. Matsuno, Oxidation of linoleic acid encapsulated with gum arabic or maltodextrin by spray-drying, *J. Microencapsulation*, 19 (2002) 181-189.
- [93] J. Kim, L.J. Cote, F. Kim, W. Yuan, K.R. Shull, J. Huang, Graphene oxide sheets at interfaces, *JACS*, 132 (2010) 8180-8186.
- [94] P. Joyce, H. Gustafsson, C.A. Prestidge, Enhancing the lipase-mediated bioaccessibility of omega-3 fatty acids by microencapsulation of fish oil droplets within porous silica particles, *J. Funct. Foods*, 47 (2018) 491-502.
- [95] L.J. Cote, J. Kim, V.C. Tung, J. Luo, F. Kim, J. Huang, Graphene oxide as surfactant sheets, *Pure Appl. Chem.*, 83 (2010) 95-110.
- [96] M.A. Creighton, W. Zhu, F. van Krieken, R.A. Petteruti, H. Gao, R.H. Hurt, Three-dimensional graphene-based microbarriers for controlling release and reactivity in colloidal liquid phases, *ACS nano*, 10 (2016) 2268-2276.
- [97] R.V. Tikekar, Y. Pan, N. Nitin, Fate of curcumin encapsulated in silica nanoparticle stabilized Pickering emulsion during storage and simulated digestion, *Food Res. Int.*, 51 (2013) 370-377.
- [98] Y. Thabet, J. Walsh, J. Breitreutz, Flexible and precise dosing of enalapril maleate for all paediatric age groups utilizing orodispersible minitablets, *Int. J. Pharm.*, 541 (2018) 136-142.
- [99] P. Mistry, H. Batchelor, Evidence of acceptability of oral paediatric medicines: a review, *J. Pharm. Pharmacol.*, 69 (2017) 361-376.
- [100] E.T. Cole, D. Cadé, H. Benameur, Challenges and opportunities in the encapsulation of liquid and semi-solid formulations into capsules for oral administration, *Adv. Drug Del. Rev.*, 60 (2008) 747-756.

- [101] Y. Ito, T. Kusawake, M. Ishida, R. Tawa, N. Shibata, K. Takada, Oral solid gentamicin preparation using emulsifier and adsorbent, *J. Control. Release*, 105 (2005) 23-31.
- [102] L. Boltri, N. Coceani, D.D. Curto, L. Dobetti, P. Esposito, Enhancement and modification of etoposide release from crospovidone particles loaded with oil-surfactant blends, *Pharm. Dev. Technol.*, 2 (1997) 373-381.
- [103] D.W. Kim, J.H. Kang, D.H. Oh, C.S. Yong, H.-G. Choi, Development of novel flurbiprofen-loaded solid self-microemulsifying drug delivery system using gelatin as solid carrier, *J. Microencapsulation*, 29 (2012) 323-330.
- [104] A. Seo, P. Holm, H.G. Kristensen, T. Schæfer, The preparation of agglomerates containing solid dispersions of diazepam by melt agglomeration in a high shear mixer, *Int. J. Pharm.*, 259 (2003) 161-171.
- [105] A. Seo, T. Schæfer, Melt agglomeration with polyethylene glycol beads at a low impeller speed in a high shear mixer, *Eur. J. Pharm. Biopharm.*, 52 (2001) 315-325.
- [106] M.K. Gupta, D. Goldman, R.H. Bogner, Y.-C. Tseng, Enhanced drug dissolution and bulk properties of solid dispersions granulated with a surface adsorbent, *Pharm. Dev. Technol.*, 6 (2001) 563-572.
- [107] S.L. Shimpi, B. Chauhan, K. Mahadik, A. Paradkar, Stabilization and improved in vivo performance of amorphous etoricoxib using Gelucire 50/13, *Pharm. Res.*, 22 (2005) 1727-1734.
- [108] M. Krstic, J. Djuris, O. Petrovic, N. Lazarevic, S. Cvijic, S. Ibric, Application of the melt granulation technique in development of lipid matrix tablets with immediate release of carbamazepine, *J. Drug Deliv. Sci. Technol.*, 39 (2017) 467-474.
- [109] R. Yasmin, A. Tan, K.E. Bremmell, C.A. Prestidge, Lyophilized Silica Lipid Hybrid (SLH) Carriers for Poorly Water-Soluble Drugs: Physicochemical and In Vitro Pharmaceutical Investigations, *J. Pharm. Sci.*, 103 (2014) 2950-2959.
- [110] S.K. Singh, P.R. Vuddanda, S. Singh, A.K. Srivastava, A comparison between use of spray and freeze drying techniques for preparation of solid self-microemulsifying formulation of valsartan and in vitro and in vivo evaluation, *BioMed Res. Int.*, 2013 (2013).
- [111] T.R. Meola, T.J. Dening, C.A. Prestidge, Nanocrystal-Silica-Lipid Hybrid Particles for the Improved Oral Delivery of Ziprasidone in vitro, *Eur. J. Pharm. Biopharm.*, (2018).
- [112] V. Bala, S. Rao, C.A. Prestidge, Facilitating gastrointestinal solubilisation and enhanced oral absorption of SN38 using a molecularly complexed silica-lipid hybrid delivery system, *Eur. J. Pharm. Biopharm.*, 105 (2016) 32-39.
- [113] T.-H. Nguyen, A. Tan, L. Santos, D. Ngo, G.A. Edwards, C.J.H. Porter, C.A. Prestidge, B.J. Boyd, Silica-lipid hybrid (SLH) formulations enhance the oral bioavailability and efficacy of celecoxib: An in vivo evaluation, *J. Control. Release*, 167 (2013) 85-91.
- [114] T. Hansen, P. Holm, K. Schultz, Process characteristics and compaction of spray-dried emulsions containing a drug dissolved in lipid, *Int. J. Pharm.*, 287 (2004) 55-66.
- [115] P. Balakrishnan, B.-J. Lee, D.H. Oh, J.O. Kim, M.J. Hong, J.-P. Jee, J.A. Kim, B.K. Yoo, J.S. Woo, C.S. Yong, Enhanced oral bioavailability of dexibuprofen by a novel solid self-emulsifying drug delivery system (SEDDS), *Eur. J. Pharm. Biopharm.*, 72 (2009) 539-545.
- [116] M.R. Rao, S.S. Aghav, Spray-Dried Redispersible Emulsion to Improve Oral Bioavailability of Itraconazole, *Journal of Surfactants and Detergents*, 17 (2014) 807-817.
- [117] I.-h. Baek, J.-S. Kim, E.-S. Ha, G.-H. Choo, W. Cho, S.-J. Hwang, M.-S. Kim, Oral absorption of a valsartan-loaded spray-dried emulsion based on hydroxypropylmethyl cellulose, *Int. J. Biol. Macromol.*, 69 (2014) 222-228.

- [118] A. Tan, N.G. Eskandar, S. Rao, C.A. Prestidge, First in man bioavailability and tolerability studies of a silica-lipid hybrid (Lipoceramic) formulation: a Phase I study with ibuprofen, *Drug Deliv. Transl. Res.*, 4 (2014) 212.
- [119] T.J. Dening, S. Rao, N. Thomas, C.A. Prestidge, Montmorillonite-lipid hybrid carriers for ionizable and neutral poorly water-soluble drugs: Formulation, characterization and in vitro lipolysis studies, *Int. J. Pharm.*, 526 (2017) 95-105.
- [120] D.H. Truong, T.H. Tran, T. Ramasamy, J.Y. Choi, H.H. Lee, C. Moon, H.-G. Choi, C.S. Yong, J.O. Kim, Development of solid self-emulsifying formulation for improving the oral bioavailability of erlotinib, *AAPS PharmSciTech*, 17 (2016) 466-473.
- [121] M.J. Kang, S.Y. Jung, W.H. Song, J.S. Park, S.-U. Choi, K.T. Oh, H.-K. Choi, Y.W. Choi, J. Lee, B.-J. Lee, Immediate release of ibuprofen from Fujicalin®-based fast-dissolving self-emulsifying tablets, *Drug Dev. Ind. Pharm.*, 37 (2011) 1298-1305.
- [122] G. Quan, Q. Wu, X. Zhang, Z. Zhan, C. Zhou, B. Chen, Z. Zhang, G. Li, X. Pan, C. Wu, Enhancing in vitro dissolution and in vivo bioavailability of fenofibrate by solid self-emulsifying matrix combined with SBA-15 mesoporous silica, *Colloids Surf. B*, 141 (2016) 476-482.
- [123] A. Azadeh, T. Angel, R. Shasha, A.P. Clive, Impact of Solidification on the Performance of Lipid-based Colloidal Carriers: Oil-based versus Self-emulsifying Systems, *Curr. Drug Del.*, 12 (2015) 16-25.
- [124] V. Agarwal, A. Siddiqui, H. Ali, S. Nazzal, Dissolution and powder flow characterization of solid self-emulsified drug delivery system (SEDDS), *Int. J. Pharm.*, 366 (2009) 44-52.
- [125] M. Van Speybroeck, H.D. Williams, T.-H. Nguyen, M.U. Anby, C.J. Porter, P. Augustijns, Incomplete desorption of liquid excipients reduces the in vitro and in vivo performance of self-emulsifying drug delivery systems solidified by adsorption onto an inorganic mesoporous carrier, *Mol. Pharm.*, 9 (2012) 2750-2760.
- [126] H.D. Williams, M. Van Speybroeck, P. Augustijns, C.J. Porter, Lipid-based formulations solidified via adsorption onto the mesoporous carrier Neusilin® US2: Effect of drug type and formulation composition on in vitro pharmaceutical performance, *J. Pharm. Sci.*, 103 (2014) 1734-1746.
- [127] T.J. Dening, S. Rao, N.D. Thomas, C.A. Prestidge, Novel nanostructured solid materials for modulating oral drug delivery from solid-state lipid-based drug delivery systems, *AAPS journal*, (2015) 1-18.
- [128] O.M. Feeney, M.F. Crum, C.L. McEvoy, N.L. Trevaskis, H.D. Williams, C.W. Pouton, W.N. Charman, C.A. Bergström, C.J. Porter, 50 years of oral lipid-based formulations: provenance, progress and future perspectives, *Adv. Drug Del. Rev.*, 101 (2016) 167-194.
- [129] D.M. Parikh, *Handbook of pharmaceutical granulation technology*, CRC Press 2016.
- [130] H. Patil, R.V. Tiwari, M.A. Repka, Hot-melt extrusion: from theory to application in pharmaceutical formulation, *AAPS PharmSciTech*, 17 (2016) 20-42.
- [131] X.C. Tang, M.J. Pikal, Design of freeze-drying processes for pharmaceuticals: practical advice, *Pharm. Res.*, 21 (2004) 191-200.
- [132] M.K. Lee, M.Y. Kim, S. Kim, J. Lee, Cryoprotectants for freeze drying of drug nano-suspensions: Effect of freezing rate, *J. Pharm. Sci.*, 98 (2009) 4808-4817.
- [133] S. Huang, K.P. O'Donnell, J.M. Keen, M.A. Rickard, J.W. McGinity, R.O. Williams, A new extrudable form of hypromellose: AFFINISOL™ HPMC HME, *AAPS PharmSciTech*, 17 (2016) 106-119.

- [134] S. Hengsawas Surasarang, J.M. Keen, S. Huang, F. Zhang, J.W. McGinity, R.O. Williams III, Hot melt extrusion versus spray drying: hot melt extrusion degrades albandazole, *Drug Dev. Ind. Pharm.*, 43 (2017) 797-811.
- [135] D.J. Hauss, Oral lipid-based formulations: enhancing the bioavailability of poorly water-soluble drugs, CRC Press 2007.
- [136] J. Bamba, G. Cave, Y. Bensouda, P. Tchoreloff, F. Puisieux, G. Couarraze, Cryoprotection of emulsions in freeze-drying: freezing process analysis, *Drug Dev. Ind. Pharm.*, 21 (1995) 1749-1760.
- [137] A. Tan, C.A. Prestidge, Improving the Performance of Lipid Formulations: Nanoparticle Layers and Solid Hybrid Particles, *American Pharmaceutical Review*, (2013).
- [138] J. Mandić, A.Z. Pobirk, F. Vrečer, M. Gašperlin, Overview of solidification techniques for self-emulsifying drug delivery systems from industrial perspective, *Int. J. Pharm.*, 533 (2017) 335-345.
- [139] A. Tan, Davey, A.K., Prestidge, C.A., Silica-Lipid Hybrid (SLH) *Versus* Non-lipid Formulations for Optimising the Dose-Dependent Oral Absorption of Celecoxib, *Pharm. Res.*, 28 (2011) 2273-2287.
- [140] S. Fernandez, S. Chevrier, N. Ritter, B. Mahler, F. Demarne, F. Carrière, V. Jannin, In Vitro Gastrointestinal Lipolysis of Four Formulations of Piroxicam and Cinnarizine with the Self Emulsifying Excipients Labrasol® and Gelucire® 44/14, *Pharm. Res.*, 26 (2009) 1901-1910.
- [141] M. Armand, Lipases and lipolysis in the human digestive tract: where do we stand?, *Curr. Opin. Clin. Nutr. Metab. Care*, 10 (2007) 156.
- [142] R.D. Schmid, R. Verger, Lipases: Interfacial Enzymes with Attractive Applications, *Angew. Chem. Int. Ed.*, 37 (1998) 1608-1633.
- [143] P. Reis, Holmberg, K., Watzke, H., Leser, M.E., Miller, R., Lipases at interfaces: a review, *Adv. Colloid Interface Sci.*, 147-148 (2009) 237-250.
- [144] P. Joyce, C.P. Whitby, C.A. Prestidge, Nanostructuring Biomaterials with Specific Activities towards Digestive Enzymes for Controlled Gastrointestinal Absorption of Lipophilic Bioactive Molecules, *Adv. Colloid Interface Sci.*, 237 (2016) 52-75.
- [145] P. Joyce, T.J. Dening, H. Gustafsson, C.A. Prestidge, Modulating the lipase-mediated bioactivity of particle-lipid conjugates through changes in nanostructure and surface chemistry, *Eur. J. Lipid Sci. Technol.*, 119 (2017) 1700213-1700222.
- [146] P. Joyce, A. Tan, C.P. Whitby, C.A. Prestidge, The Role of Porous Nanostructure in Controlling Lipase-Mediated Digestion of Lipid Loaded into Silica Particles, *Langmuir*, 30 (2014) 2779-2788.
- [147] P. Joyce, C.P. Whitby, C.A. Prestidge, Interfacial processes that modulate the kinetics of lipase-mediated catalysis using porous silica host particles, *RSC Adv.*, 6 (2016) 43802-43813.
- [148] P. Joyce, H. Gustafsson, C.A. Prestidge, Engineering intelligent particle-lipid composites that control lipase-mediated digestion, *Adv. Colloid Interface Sci.*, submitted (2017).
- [149] P. Joyce, T. Barnes, B. Boyd, C.A. Prestidge, Porous Nanostructure Controls Kinetics, Disposition and Self-Assembly Structure of Lipid Digestion Products, *RSC Adv.*, 6 (2016) 78385-78395.
- [150] A. Tan, Simovic, S., Davey, A.K., Rades, T., Boyd, B.J., Prestidge, C.A., Silica Nanoparticles To Control the Lipase-Mediated Digestion of Lipid-Based Oral Delivery Systems, *Mol. Pharm.*, 7 (2010) 522-532.

- [151] A. Tan, P. Colliat-Dangus, C.P. Whitby, C.A. Prestidge, Controlling the Enzymatic Digestion of Lipids Using Hybrid Nanostructured Materials, *ACS Appl. Mater. Interfaces*, 6 (2014) 15363-15371.
- [152] J. Xiao, C. Li, Q. Huang, Kafirin Nanoparticle-Stabilized Pickering Emulsions as Oral Delivery Vehicles: Physicochemical Stability and *in vitro* Digestion Profile, *J. Agric. Food. Chem.*, 63 (2015) 10263-10270.
- [153] T.J. Dening, P. Joyce, S. Rao, N. Thomas, C.A. Prestidge, Nanostructured Montmorillonite Clay for Controlling the Lipase-Mediated Digestion of Medium Chain Triglycerides, *ACS Appl. Mater. Interfaces*, 8 (2016) 32732-32742.
- [154] M.V. Tzoumaki, T. Moschakis, E. Scholten, C.G. Biliaderis, *In vitro* lipid digestion of chitin nanocrystal stabilized o/w emulsions, *Food Funct.*, 4 (2012) 121-129.
- [155] Y. Li, Hu, M., McClements, D.J., Factors affecting lipase digestibility of emulsified lipids using an *in vitro* digestion model: Proposal for a standardised pH-stat method, *Food Chem.*, 126 (2011) 498-505.
- [156] U. Lesmes, D.J. McClements, Controlling lipid digestibility: Response of lipid droplets coated by [beta]-lactoglobulin-dextran Maillard conjugates to simulated gastrointestinal conditions, *Food Hydrocoll.*, 26 (2012) 221.
- [157] Y. Li, D.J. McClements, Controlling lipid digestion by encapsulation of protein-stabilized lipid droplets within alginate-chitosan complex coacervates, *Food Hydrocoll.*, 25 (2011) 1025-1033.
- [158] Y. Park, G.Y. Park, Y. Park, S. Mun, S. Rhee, E.A. Decker, J. Weiss, D.J. McClements, Influence of encapsulation of emulsified lipids with chitosan on their *in vivo* digestibility, *Food Chem.*, 104 (2007) 761-767.
- [159] S. Mun, E.A. Decker, Y. Park, J. Weiss, D.J. McClements, Influence of Interfacial Composition on *in vitro* Digestibility of Emulsified Lipids: Potential Mechanism for Chitosan's Ability to Inhibit Fat Digestion, *Food Biophys.*, 1 (2006) 21-29.
- [160] R. Liang, Y. Jiang, W. Yokoyama, C. Yang, G. Cao, F. Zhong, Preparation of Pickering emulsions with short, medium and long chain triacylglycerols stabilized by starch nanocrystals and their *in vitro* digestion properties, *RSC Adv.*, 6 (2016) 99496-99508.
- [161] P. Reis, K. Holmberg, T. Debeche, B. Folmer, L. Fauconnot, H. Watzke, Lipase-catalyzed reactions at different surfaces, *Langmuir*, 22 (2006) 8169-8177.
- [162] P. Joyce, I. Kempson, C.A. Prestidge, Orientating Lipase Molecules through Surface Chemical Control for Enhanced Activity: A QCM-D and ToF-SIMS Investigation, *Colloids Surf. B*, 142 (2016) 173-181.
- [163] P. Joyce, I. Kempson, C.A. Prestidge, QCM-D and ToF-SIMS Investigation to Deconvolute the Relationship between Lipid Adsorption and Orientation on Lipase Activity, *Langmuir*, 31 (2015) 10198-10207.
- [164] P. Reis, K. Holmberg, R. Miller, M.E. Leser, T. Raab, H.J. Watzke, Lipase reaction at interfaces as self-limiting processes, *Comptes Rendus Chimie*, 12 (2009) 163-170.
- [165] P. Reis, H. Watzke, M. Leser, K. Holmberg, R. Miller, Interfacial mechanism of lipolysis as self-regulated process, *Biophys. Chem.*, 147 (2010) 93-103.
- [166] P. Reis, K. Holmberg, R. Miller, J. Krägel, D.O. Grigoriev, M.E. Leser, H.J. Watzke, Competition between lipases and monoglycerides at interfaces, *Langmuir*, 24 (2008) 7400-7407.
- [167] T.J. Dening, P. Joyce, C.A. Prestidge, Improving correlations between *in vitro* lipophilic drug solubilization and lipase-mediated digestion kinetics by monitoring FFA partitioning, *J. Pharm. Sci.*, *In press*. (2018).

- [168] M. Koziolk, F. Carrière, C.J.H. Porter, Lipids in the Stomach – Implications for the Evaluation of Food Effects on Oral Drug Absorption, *Pharm. Res.*, 35 (2018) 55.
- [169] M. Koziolk, G. Garbacz, M. Neumann, W. Weitschies, Simulating the postprandial stomach: physiological considerations for dissolution and release testing, *Mol. Pharm.*, 10 (2013) 1610-1622.
- [170] M. Golding, Wooster, T.J., Day, L., Xu, M., Lundin, L., Keogh, J., Impact of gastric structuring on the lipolysis of emulsified lipids, *Soft Matter*, 7 (2011) 3513-3523.
- [171] M. Golding, T.J. Wooster, The influence of emulsion structure and stability on lipid digestion, *Curr. Opin. Colloid Interface Sci.*, 15 (2010) 90-101.
- [172] H.B. Kennogne-domguia, A. Meynier, M. Viau, G. Llamas, C. Genot, Gastric conditions control both the evolution of the organization of protein-stabilized emulsions and the kinetic of lipolysis during in vitro digestion, *Food & Function*, 3 (2012) 1302-1309.
- [173] F. Carrière, Digestive processes in the GI tract and their impact on the fate of oral drugs and formulations, 2018.
- [174] K.W.Y. Lee, C.J.H. Porter, B.J. Boyd, Gastric Pre-Processing Is an Important Determinant of the Ability of Medium-Chain Lipid Solution Formulations to Enhance Oral Bioavailability in Rats, *J. Pharm. Sci.*, 102 (2013) 3957-3965.
- [175] C. Eydoux, S. Spinelli, T.L. Davis, J.R. Walker, A. Seitova, S. Dhe-Paganon, A. De Caro, C. Cambillau, F. Carrière, Structure of human pancreatic lipase-related protein 2 with the lid in an open conformation, *Biochemistry*, 47 (2008) 9553-9564.
- [176] S. Ransac, F. Carrière, E. Rogalska, R. Verger, F. Marguet, G. Buono, E. Pinho Melo, J.S. Cabral, M.-P. Egloff, H. Tübeurgh, C. Cambillau, The Kinetics, Specificities and Structural Features of Lipases, in: J.F. Op den Kamp (Ed.) *Molecular Dynamics of Biomembranes*, Springer Berlin Heidelberg 1996, pp. 265-304.
- [177] F. Carrière, Impact of gastrointestinal lipolysis on oral lipid-based formulations and bioavailability of lipophilic drugs, 2015.
- [178] M. Chatzidaki, E. Mateos-Diaz, F. Leal-Calderon, A. Xenakis, F. Carrière, Water-in-oil microemulsions: Versus emulsions as carriers of hydroxytyrosol: An in vitro gastrointestinal lipolysis study using the pHstat technique, 2016.
- [179] D.H. Oh, J.H. Kang, D.W. Kim, B.-J. Lee, J.O. Kim, C.S. Yong, H.-G. Choi, Comparison of solid self-microemulsifying drug delivery system (solid SMEDDS) prepared with hydrophilic and hydrophobic solid carrier, *Int. J. Pharm.*, 420 (2011) 412-418.
- [180] J.H. Kang, D.H. Oh, Y.-K. Oh, C.S. Yong, H.-G. Choi, Effects of solid carriers on the crystalline properties, dissolution and bioavailability of flurbiprofen in solid self-nanoemulsifying drug delivery system (solid SNEDDS), *Eur. J. Pharm. Biopharm.*, 80 (2012) 289-297.
- [181] A. Aina, A. Morris, M. Gupta, N. Billa, N. Madhvani, R. Sharma, S. Doughty, V. Shah, Y. Boukari, Dissolution behavior of poly vinyl alcohol in water and its effect on the physical morphologies of PLGA scaffolds, *UK JPB*, 2 (2014) 1-6.
- [182] J.-H. Guo, G. Skinner, W. Harcum, P. Barnum, Pharmaceutical applications of naturally occurring water-soluble polymers, *Pharm. Sci. Technol. Today*, 1 (1998) 254-261.
- [183] A.V. Shah, A.T. Serajuddin, Development of solid self-emulsifying drug delivery system (SEDDS) I: use of poloxamer 188 as both solidifying and emulsifying agent for lipids, *Pharm. Res.*, 29 (2012) 2817-2832.
- [184] T. Yi, J. Wan, H. Xu, X. Yang, Controlled poorly soluble drug release from solid self-microemulsifying formulations with high viscosity hydroxypropylmethylcellulose, *Eur. J. Pharm. Sci.*, 34 (2008) 274-280.

- [185] P. Zhang, J. Forsgren, M. Strømme, Stabilisation of amorphous ibuprofen in Upsalite, a mesoporous magnesium carbonate, as an approach to increasing the aqueous solubility of poorly soluble drugs, *Int. J. Pharm.*, 472 (2014) 185-191.
- [186] P. Zhang, T.Z.G. de la Torre, J. Forsgren, C.A. Bergström, M. Strømme, Diffusion-controlled drug release from the mesoporous magnesium carbonate Upsalite®, *J. Pharm. Sci.*, 105 (2016) 657-663.
- [187] Y. Ueno, H. Futagawa, Y. Takagi, A. Ueno, Y. Mizushima, Drug-incorporating calcium carbonate nanoparticles for a new delivery system, *J. Control. Release*, 103 (2005) 93-98.
- [188] Y. Svenskaya, B. Parakhonskiy, A. Haase, V. Atkin, E. Lukyanets, D. Gorin, R. Antolini, Anticancer drug delivery system based on calcium carbonate particles loaded with a photosensitizer, *Biophys. Chem.*, 182 (2013) 11-15.
- [189] T. Riis, A. Bauer-Brandl, T. Wagner, H. Kranz, pH-independent drug release of an extremely poorly soluble weakly acidic drug from multiparticulate extended release formulations, *Eur. J. Pharm. Biopharm.*, 65 (2007) 78-84.
- [190] G.B. Sukhorukov, D.V. Volodkin, A.M. Günther, A.I. Petrov, D.B. Shenoy, H. Möhwald, Porous calcium carbonate microparticles as templates for encapsulation of bioactive compounds, *J. Mater. Chem.*, 14 (2004) 2073-2081.
- [191] Y. Weerapol, S. Limmatvapirat, J. Nunthanid, P. Sriamornsak, Self-nanoemulsifying drug delivery system of nifedipine: impact of hydrophilic-lipophilic balance and molecular structure of mixed surfactants, *AAPS PharmSciTech*, 15 (2014) 456-464.
- [192] C. Sauzet, M. Claeys-Bruno, M. Nicolas, J. Kister, P. Piccerelle, P. Prinderre, An innovative floating gastro retentive dosage system: Formulation and in vitro evaluation, *Int. J. Pharm.*, 378 (2009) 23-29.
- [193] K. Unger, D. Kumar, M. Grün, G. Büchel, S. Lüdtke, T. Adam, K. Schumacher, S. Renker, Synthesis of spherical porous silicas in the micron and submicron size range: challenges and opportunities for miniaturized high-resolution chromatographic and electrokinetic separations, *J. Chromatogr.*, 892 (2000) 47-55.
- [194] R. Schoonheydt, C. Johnston, Surface and interface chemistry of clay minerals, *Developments in clay science*, 1 (2006) 87-113.
- [195] E.M. Pecini, M.J. Avena, Measuring the isoelectric point of the edges of clay mineral particles: The case of montmorillonite, *Langmuir*, 29 (2013) 14926-14934.
- [196] S.G. Gumaste, S.A. Pawlak, D.M. Dalrymple, C.J. Nider, L.D. Trombetta, A.T.M. Serajuddin, Development of Solid SEDDS, IV: Effect of Adsorbed Lipid and Surfactant on Tableting Properties and Surface Structures of Different Silicates, *Pharm. Res.*, 30 (2013) 3170-3185.
- [197] S.G. Gumaste, D.M. Dalrymple, A.T. Serajuddin, Development of solid SEDDS, V: compaction and drug release properties of tablets prepared by adsorbing lipid-based formulations onto Neusilin® US2, *Pharm. Res.*, 30 (2013) 3186-3199.
- [198] T.J. Dening, P. Joyce, J.L. Webber, D.A. Beattie, C.A. Prestidge, Carrier Surface Chemistry and Nanostructure Controls Lipolytic Product Speciation and Partitioning During the Digestion of Inorganic-Lipid Hybrid Particles, *J. Colloid Interface Sci.*, submitted. (2018).
- [199] R.B. Chavan, S.R. Modi, A.K. Bansal, Role of solid carriers in pharmaceutical performance of solid supersaturable SEDDS of celecoxib, *Int. J. Pharm.*, 495 (2015) 374-384.
- [200] P.C. Christophersen, M.L. Christiansen, R. Holm, J. Kristensen, J. Jacobsen, B. Abrahamsson, A. Müllertz, Fed and fasted state gastro-intestinal in vitro lipolysis: In vitro in

vivo relations of a conventional tablet, a SNEDDS and a solidified SNEDDS, *Eur. J. Pharm. Sci.*, 57 (2014) 232-239.

[201] A. Krupa, J. Szłęk, B.R. Jany, R. Jachowicz, Preformulation studies on solid self-emulsifying systems in powder form containing magnesium aluminometasilicate as porous carrier, *AAPS PharmSciTech*, 16 (2015) 623-635.

[202] E. Schirm, H. Tobi, T.W. Vries, I. Choonara, L.T.W. De Jong-van den Berg, Lack of appropriate formulations of medicines for children in the community, *Acta Paediatr.*, 92 (2007) 1486-1489.

[203] A. Hassanzadeh, M. Nitsche, S. Mittler, S. Armstrong, J. Dixon, U. Langbein, Waveguide evanescent field fluorescence microscopy: thin film fluorescence intensities and its application in cell biology, *Appl. Phys. Lett.*, 92 (2008) 233503.

[204] D.A. Beattie, J. Addai-Mensah, A. Beaussart, G.V. Franks, K.-Y. Yeap, In situ particle film ATR FTIR spectroscopy of poly (N-isopropyl acrylamide)(PNIPAM) adsorption onto talc, *Phys. Chem. Chem. Phys.*, 16 (2014) 25143-25151.

[205] T.J. Barnes, I.M. Kempson, C.A. Prestidge, Surface analysis for compositional, chemical and structural imaging in pharmaceuticals with mass spectrometry: A ToF-SIMS perspective, *Int. J. Pharm.*, 417 (2011) 61-69.

[206] A.M. Belu, M.C. Davies, J.M. Newton, N. Patel, TOF-SIMS characterization and imaging of controlled-release drug delivery systems, *Anal. Chem.*, 72 (2000) 5625-5638.

[207] I.M. Kempson, A.L. Martin, J.A. Denman, P.W. French, C.A. Prestidge, T.J. Barnes, Detecting the presence of denatured human serum albumin in an adsorbed protein monolayer using TOF-SIMS, *Langmuir : the ACS journal of surfaces and colloids*, 26 (2010) 12075.

[208] K. Awsiuk, A. Budkowski, A. Psarouli, P. Petrou, A. Bernasik, S. Kakabakos, J. Rysz, I. Raptis, Protein adsorption and covalent bonding to silicon nitride surfaces modified with organo-silanes: Comparison using AFM, angle-resolved XPS and multivariate ToF-SIMS analysis, *Colloids Surf. B*, 110 (2013) 217-224.

[209] A.L. Hook, P.M. Williams, M.R. Alexander, D.J. Scurr, Multivariate ToF-SIMS image analysis of polymer microarrays and protein adsorption, *Biointerphases*, 10 (2015) 019005.